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THE CLASSIFICATION OF ECZEMATOID ERUPTIONS IN CHILDREN WITH ESPECIAL REFERENCE TO CONTACT DERMATITIS

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THIS discussion is concerned with an attempt to classify a series of 156 cases of "eczema" in children between the ages of 1 and 17 years, seen in private practice, and particularly with an inquiry into the frequency, criteria for diagnosis, and specific causes of contact dermatitis in this age group.

It is generally agreed that the skin reaction which is commonly called eczema or eczematoid dermatitis, whether it be in the infant, child, or adult, comprises several fairly distinct nosologic entities, which can, to a reasonably satisfactory degree, be separated and therefore classified. The older entirely anatomic classifications which were in vogue when but little was known of pathogenesis have been discarded by most dermatologists. In spite of this, if one studies the current textbooks of dermatology and the numerous papers by dermatologists especially interested in eczema, it is apparent that there is even now no uniformity in nomenclature or classification.

It has seemed to me that with slight modifications the nomenclature and classification suggested by Sulzberger[1] is very satisfactory for children.

In this series of 156 patients, 110 were between 1 and 4 years of age and 46 between 4 and 17 years. They were classified as follows:

Atopic dermatitis	105
Contact dermatitis	31
Fungus infection	11
Seborrhoeic dermatitis	4
Nummular eczema	3
Circumscribed neurodermatitis	2

1. Atopic Dermatitis.—The conception "atopy" as originally proposed by Coca (1922) is not held in favor by all dermatologists and allergists. I do not wish to discuss atopy. No matter whether this conception is valid or not, the term atopic dermatitis represents a useful and accu-

rately descriptive nomenclature to apply to a well-defined clinical and immunologic condition which is as much a distinct entity as diabetes is. This terminology has been adopted by some dermatologists and by many allergists.

Atopic dermatitis is defined as follows:

A dermatitis often but not necessarily always determined by hereditary predisposition, characterized by a hypersensitivity of the deeper layers of the skin (true cutis), to protein or proteinlike allergens. This hypersensitivity is usually manifested by wheal reactions of the immediate type to scratch or intracutaneous tests with these allergens. The responsible allergens may reach the sensitized tissue by ingestion or inhalation or occasionally by direct contact. Atopic dermatitis has as its basis a constitutional abnormality, the various manifestations of which (hay fever, asthma, dermatitis) may last during most of the life of the individual.

TABLE I

ATOPIC DERMATITIS (105 CASES)

1 to 4 years	74 (70.4%)
4 to 17 years	31 (29.5%)
Family history of allergy present	55 (52.3%)
SCRATCH OR INTRACUTANEOUS TESTS DONE ON 94	
Positive	77 (81.6%)
Negative	17 (18.4%)

With the older morphologic classifications, this disorder was called by many names according to the particular stage of dermatitis present, which varies greatly at different age periods. Thus, according to some dermatologists, particularly in Europe, in infancy it would be called eczema, because vesiculation is commonly present at this age; in later childhood when with the passage of time it has somewhat changed its appearance, it would be called disseminated neurodermatitis.

It is the same disease at all ages, and entirely irrespective of morphology, as Hopkins and Kesten[2] and Hill and Sulzberger[3] have pointed out, it is best called by the same name at all ages, whatever that name may be. Excellent discussions of nomenclature and the classification of this dermatosis, although it was not then called atopic dermatitis, are also given by Sulzberger, Spain, Sammis, and Shahon,[4] and by Blumenthal and Jaffé,[5] who were among the first to give it a clear place in classification.

Although at times the eruption of atopic dermatitis cannot be mistaken for anything else, it is very variable in character, and it is the soil upon which it develops and the type of allergen involved which are most important in determining its place in classification. It is a most difficult and often unsatisfactory condition to treat, knowledge of its exact mechanism is as yet not good, and it is not always easy to differentiate it from other dermatoses. As far as classification goes, however, it stands clear and sharp.

It is primarily a disease of the young. Over 50 per cent of the 105 patients in the series under discussion were between 1 and 3 years of age. At this age period it is particularly difficult to treat for many reasons which I will not discuss, and I think, also, that it is harder to classify accurately in this age period than in a later age. Skin testing, which is often of importance in classification, is in young children so unpleasant for everyone concerned that it is difficult to do as completely or as accurately as it can be done with older children or adults. Scratch tests with all the common food and environmental allergens can be done almost always if one is willing to put up with a good deal of disturbance. Occasionally a stouthearted 2- or 3-year-old child is so refractory that no satisfactory testing can be done. It is not desirable, on account of the danger, which is not great but ever present, of producing a systemic reaction by intracutaneous tests, to do these without previously having obtained negative scratch tests to the allergens in question. Therefore, if a complete set of intracutaneous tests is attempted, a great deal of testing is necessitated, which in a struggling young child is simply not sensible or practical and is usually not worth the amount of disturbance involved. On the other hand, if negative scratch tests are not followed by intracutaneous, significant reactions may be missed, particularly with some of the less active allergens (milk, feathers, dust). The more active allergens (egg, fish, nuts, horse dander) will give positive scratch tests in a high percentage of patients if they react at all. My practice with young children is to do scratch tests with about forty allergens, in two sittings, and if these reveal nothing of significance, to follow them with a few intracutaneous tests with allergens which according to circumstances may be important. I have no routine for intracutaneous tests except with milk for young babies. Such testing, from a research point of view, is not as accurate as it might be; from a practical point of view it does reasonably well. Routine intracutaneous testing with a large number of allergens in children under 4 years of age is not practical in my experience. The indirect method of testing I use occasionally but for many reasons have not found it desirable to employ as a routine.

I do not wish to discuss the significance or value of skin tests except in so far as they apply to classification. Normal children do not give positive scratch tests. If scratch tests are positive, the child can be put immediately into the atopic group. This means usually but not always that the presenting dermatitis is atopic dermatitis, for, as will be pointed out later, an acute contact dermatitis due to a different mechanism and allergens of a different type may occasionally add itself to a chronic atopic dermatitis so that the patient may be suffering from two unrelated kinds of dermatitis at the same time. Normal infants do not have either positive scratch or intracutaneous tests, except sometimes for short periods (intracutaneous) after the taking of a new food. I know of no data for intracutaneous tests in normal

children. It is my belief that it is not abnormal for any adult to show positive intracutaneous tests to protein allergens. The reasons for this I discussed in 1940.[6] Not all would agree with this. The older the child, the more do positive intracutaneous tests tend to assume the same significance that they do in the adult. It is reasonable to assume, therefore, that for purposes of classification, positive intracutaneous tests in children do not have as much significance as positive scratch tests.

The allergens concerned in atopic dermatitis may work by ingestion, inhalation, or occasionally by *direct contact* through an injured epidermis, or more rarely, and I think very rarely, by penetration of an intact epidermis. Here then arises some confusion in nomenclature. When the allergens responsible for atopic dermatitis produce dermatitis by direct contact (wool, silk), why should not such an eruption be called contact dermatitis? Because the term contact dermatitis has been reserved for a different condition which, although it may sometimes closely resemble atopic dermatitis in appearance, has enough immunologic and clinical differences to warrant separate classification. The allergens of atopic dermatitis are of protein character, wheals are produced by scratch or intracutaneous tests, the sensitization is not of the epidermis but of the small vessels in the upper portion of the cutis, patch tests are as a rule negative, and if the sensitization is of high degree (silk), urticaria and not vesiculation is produced by contact. All these criteria are different from those demanded of contact dermatitis.

When the allergens of atopic dermatitis work by contact, it is best, in order to avoid confusion, to term such eruptions atopic dermatitis by contact, rather than contact dermatitis. This may seem a quibble, but if these two types of allergic dermatitis are to be separated at all, it is no quibble.

2. Contact Dermatitis.—A dermatitis in which there is hypersensitivity of the epidermis to one or more of innumerable organic or inorganic substances of almost any chemical constitution, which are, in the concentration experienced, not irritating in the absence of allergic sensitization. Contact dermatitis also may be caused without allergic sensitization by primary irritants which on account of their intrinsically irritating properties in proper concentration cause dermatitis on all skins. The substances which cause contact dermatitis reach the skin by direct contact; scratch and intracutaneous tests are negative and patch tests are often positive. The reaction produced is erythematous, vesicular, or bullous, and is of the delayed type. Contact dermatitis, in so far as is known, is not determined by heredity, nor is it, except fortuitously, associated with other allergic manifestations, such as asthma, hay fever, or urticaria.

This is the condition for which in a strict dermatologic sense the term eczema is reserved by many dermatologists. It is the common eczema

of adult life; various forms of occupational and industrial dermatitis and that due to poison ivy are the classical examples.

It seems certain that contact dermatitis as above defined is not common in early infancy; there is little information available to indicate how common it is in childhood. The child is not exposed as a rule to the number of excitants of this type of dermatitis as is the adult. There is no reason to believe, however, that if he is exposed, his skin will not become sensitized as readily as that of the adult. Most young children are dressed in short socks, very short drawers, trousers, or dresses, and short-sleeved waists or blouses, so that large areas of skin surface are exposed. The dermatitis under discussion almost always appears on exposed areas. The most common example is a child from 2 to 4 years of age with a subacute or sometimes acute dermatitis largely confined to the arms, legs, and neck. Sometimes when the sensitization is of high degree and the irritant has reached the skin in relatively high concentration, the dermatitis may spread rapidly to the trunk, or if it has reached the blood stream, there may be a generalized eruption of small papulovesicles, some of which may be fused into large homogeneous, oozing areas. The trunk is, however, not often primarily involved. In 67 per cent of the 31 cases under discussion, the eruption began on the arms, legs, or hands. In the subacute or chronic cases there is often a sharp line of demarcation at the upper third of the arm, with dermatitis below the short sleeve, and normal skin where the arm is covered. There is also frequently a curved line of demarcation separating exposed and nonexposed areas at the neck.

TABLE II

CONTACT DERMATITIS (THIRTY-ONE CASES)

1 to 4 years	22 (70.0%)
4 to 17 years	9 (29.1%)
Family history of allergy present	9 (29.1%)
SCRATCH OR INTRACUTANEOUS TESTS DONE ON 16	
Positive	3*
Negative	13

*These three patients all had an acute contact dermatitis added to an already existing atopic dermatitis. If these are excluded, no case in this group gave positive scratch or intracutaneous tests. In those patients not tested it was obvious from the clinical history and appearance of the eruption that it was contact and not atopic dermatitis, and scratch or intracutaneous tests were not indicated.

For most of the patients classified as contact dermatitis, all sorts of experimental diets had been used without any results whatever. It is obvious that such dermatitis is of external origin. It is often very difficult, however, to decide whether it is of the atopic or contact variety, and still more difficult to determine the exact causation.

It is harder to do this in these young children than in adults because there is so often no clue whatsoever, no known exposure to eczematogenous substances. When the dermatitis appears suddenly in a local-

ized area on a previously healthy skin following exposure to some known eczematogenous material, or if it is bullous or frankly vesicular, indicating clearly its epidermal origin, these difficulties are not present. The location of the original eruption often gives a clue as to its origin, although it must be remembered that when the sensitivity is of high degree, the dermatitis may spread with considerable rapidity to areas far from the original exposure. It is, as a rule, not difficult to classify the acute cases but very difficult to classify those which are subacute or chronic.

The mother is always closely questioned about exposure to any sort of chemicals. Usually no such exposure can be found. Under suspicion also are toys, dyes in fabrics, cosmetics, and soaps, or indeed anything which may have come into contact with the child's skin. I have never seen contact dermatitis in a child that I thought was primarily due to soap, although it seems probable that soap may predispose to the development of dermatitis from some other cause or may aggravate an already existing dermatitis. According to most dermatologists, soap is a frequent cause of dermatitis of the hands, particularly in housewives.[7] I do not believe it is very important in children. Dermatitis of the hands is not so common in children, and the arm dermatitis, which is very common, seldom begins in the hands.

The one thing which comes into most frequent contact with the arms, legs, and neck of a young child is his outer winter clothing. He is smothered in snowsuits, mufflers, mittens, leggings, and blankets. It is sometimes found that the dye in some one of these articles is responsible for the dermatitis. Another possibility is naphthalene, if the clothes have been kept with moth balls in the summer. If the dermatitis is due to wool, as it undoubtedly sometimes is, it should in most cases be classified not in this group but under atopic dermatitis. Atopic sensitization to wool, sometimes of a high degree, is not uncommon. Positive scratch tests to wool are fairly common (8 per cent in a series of 100 infants and children with known atopic dermatitis); positive intracutaneous tests are very common, although their authenticity as true immunologic reactions is open to some doubt. The rough wool fiber is irritating to some skins in a purely mechanical way and may possibly cause dermatitis without the intervention of allergic sensitization or may conceivably predispose to sensitization by other substances. More accurate information is needed concerning wool as a cause of dermatitis.

Patch Tests: There is no object in doing routine patch tests on young children with all the various chemicals that are used routinely for adults, because they do not come into contact with such chemicals. My opinion of patch tests for children coincides exactly with that of Osborne and Walker,[8] who wrote the following in a splendid paper. "Patch tests in infants and very young children are of value only when two, three, or four strongly suspected contact substances can be applied to an entirely normal area adjacent to an eczematous area. Patch tests are of

value in following up leads obtained by careful study of the history and environmental and contact factors."

It is sometimes stated in dermatologic literature that patch tests are better than scratch tests. Such a statement is the same as saying that a spoon is better than a fork. A spoon is better for soup, a fork for spaghetti. Scratch tests are better for atopic dermatitis, patch tests for contact dermatitis.

If the sensitization is violent, as it so often is in ivy or mercury dermatitis, and comparatively short and slight contact will produce dermatitis, a positive patch test can be expected, for natural conditions are reproduced. It is not well, however, as Downing[9] has wisely said, to do a patch test if it is obvious from the history that the dermatitis has been produced by a known substance, for if the sensitization is of high degree, the application of the patch test may cause an exacerbation and extension of the original dermatitis. If the sensitization is not of high degree and subacute or chronic dermatitis has been produced by repeated and continuous contact, helped by rubbing or by minute abrasions in the skin from other causes which I think is often the case in young children, the patch test does not reproduce natural conditions, and there is no reason why it should be positive. I have done many patch tests on young children. I have seen a few very definite reactions which helped in diagnosis but have seen far more that were negative, even when it was clear that the substance in question was producing the dermatitis.

When one determines the exact cause of a long-standing and hitherto obscure contact eruption, removes it, and cures the patient, it is a source of great rejoicing—a very accurate and satisfying scientific experience—two plus two equals four. Unfortunately in my practice two plus two very often does not equal four. I do not know how often in dermatologic practice the exact cause of contact dermatitis in adults is determined; I have seen many reports when it was, very few when it was not. My own batting average is not high in determining exact causation in this group of patients, and having no dermatologic standing whatever I can report disappointing results without embarrassment.

In the 31 cases under discussion, the cause of the dermatitis was determined with reasonable accuracy in 15, partly by history and clinical circumstances, partly by patch tests.

These causes were as follows:*

1. Dye in snowsuit
2. Dye in snowsuit
3. Dye in snowsuit
4. Dye in sweater
5. Dye in cloth rabbit
6. Mother's cosmetics
7. Primrose
8. Ivy
9. Ivy
10. Toilet seat (lacquer)
11. Sulfur
12. Ammoniated mercury
13. "Lemon" shampoo (proprietary)
14. Furniture polish
15. Hair tonic

*In addition to these I have seen in the clinic contact dermatitis from turpentine, the leaves of the white mulberry tree, tar, creosote, and tincture of green soap.

In the remaining 16 cases it was reasonably certain that the dermatitis was not due to food but to external agents and was of the contact and not atopic variety; however, the exact cause was not found. In spite of this, some patients in the group were cured and most were helped by local treatment and the avoidance of all possible harmful contacts. There is one possible and indeed probable error in this group; some of these patients may have been suffering from atopic and not contact dermatitis. The rather high incidence of allergy in the family history of the "contact" group as a whole (29 per cent) is somewhat indicative of this, although the series is too small to make such statistics of much significance. Furthermore, scratch and intradermal tests were not done in 15 cases but were done in 16. I do not think there is much source of error in the first group because the history and characteristics of the eruption precluded the likelihood of atopic dermatitis, and for this reason scratch tests were not done. There is, however, probability of error in the second group. In this group the appearance of the dermatitis was enough like atopic dermatitis to warrant scratch tests. All were negative. Complete intracutaneous tests were not done on any patients, however, and it may well be that some of these patients should have been put into the atopic group.

I said in the discussion of atopic dermatitis that it might be complicated by an added contact dermatitis. There were 5 such patients. They have been included in the contact rather than in the atopic group. The exact cause of the complicating contact eruption was determined in all 5 cases. This situation sometimes presents a rather confusing picture and is always worth while bearing in mind when a patient with chronic atopic dermatitis has a sudden acute flare-up, usually with vesiculation, in a localized area. The general opinion is that from an immunologic point of view the individual with atopic dermatitis does not become any more easily sensitized to the substances responsible for contact dermatitis than does the normal individual. This may be so. From a practical point of view, however, I doubt if it is so because his skin is fissured and abraded, he is continually rubbing and scratching, and it is well known that a damaged skin, even if the damage is microscopic, becomes more easily sensitized than a sound skin.

The following case reports are illustrative of contact dermatitis superimposed upon an already existing atopic eruption.

CASE 1.—M. P., female, 17 years of age, had eczema of the atopic variety treated by me sixteen years ago. She gradually got over it. She has had asthma off and on ever since the age of 2 years and timothy and ragweed hay fever for the last few years. There is atopic dermatitis most of the time in front of the elbows but not bad. For four months she has had a dermatitis on the sides and back of the neck. This has remissions and exacerbations. During exacerbations it is vesicular. Examination showed an irregular, thickened, crusted, slightly oozy dermatitis covering the entire back of the neck and extending somewhat to the sides. There was also a little on the forehead. The rest of the skin was normal. Patch tests were done with (1) a brown coat, (2) a pink dress, (3) paraphenylendiamine, (4) Drene shampoo,

(5) lemon shampoo, and (6) a green dress. There was a moderately positive test with erythema and slight vesiculation to the lemon shampoo which she had been using for about six months. In about two weeks, with avoidance of the shampoo and local treatment the dermatitis was nearly healed.

CASE 2.—W. B., male, age 4½ years, was first seen Oct. 17, 1934. His eczema began at the age of 6 months and has been more or less persistent ever since. When he first took egg at the age of 1 year he broke out immediately all over. Skin tests were done by another physician at the age of 3 years, and it was said that the child had a positive reaction to egg and to nothing else. He has been on various diets at different times, without much result. The mother does not know of any food which is likely to make him worse. There is a dog in the house and a horse several houses away. He sleeps on a hair mattress of good quality and has a feather pillow. Examination showed slight roughening of the face and a moderate amount of diffuse thickening back of the knees. The rest of the skin was essentially normal. The usual scratch tests were done with a positive reaction only to horse dander. Intracutaneous tests to milk and to *Monilia albicans* were negative. He was given one x-ray treatment by a competent radiologist and was treated locally with appropriate salves and lotions.

He was next seen Jan. 9, 1935. The mother reported that the back of the knees had done very well and that he had had no eczema there for some time. About the end of November, however, he began to have a dermatitis on the inner side of both thighs. Examination showed a severe acute vesicular type of dermatitis from knees to crotch on both legs. Patch tests were done with seventeen things with which he might have come into contact. There were positive reactions to a certain soap and a blue snowsuit. Both were omitted and a mild lotion was used. In about two weeks there was scarcely a trace left of the dermatitis. Although positive patch tests were obtained to both soap and the snowsuit, there were circumstances in the history, not necessary to discuss, which made it reasonably certain that the dermatitis was due to the dye in the snowsuit and not to soap.

TABLE III

CLINICAL DIFFERENCES BETWEEN ATOPIC AND CONTACT DERMATITIS IN CHILDHOOD

	ATOPIC DERMATITIS (105 CASES)	CONTACT DERMATITIS (31 CASES)
Began under 6 mo. of age	67.7%	9.7%
Began on the face	33.3%	12.9%
Began on the arms or legs	32.3%	67.7%
Acute, with macroscopic vesiculation	5.9%	45.1%

The acute, classical, suddenly appearing type of contact dermatitis looks nothing like atopic dermatitis. The eruption is predominantly vesicular in character, or if the reaction has not been violent enough to produce vesiculation, it may be punctate, or sometimes simply erythematous. There may be a good heal of edema, particularly if the face is involved. After the age of infancy, atopic dermatitis is not often vesicular. If contact dermatitis becomes chronic, it may be indistinguishable from atopic dermatitis. Both may be manifested by diffuse or patchy reddened areas, moderately thickened, with scaling. The characteristic deep-seated papules with excoriated tops so often seen in atopic dermatitis are not seen in contact dermatitis, nor is the latter so likely to become lichenified. The reaction of contact dermatitis is more superficial.

Atopic dermatitis is common on the trunk as well as on exposed areas. Contact dermatitis is not so common on the trunk. In contact dermatitis there is often one area, where it is obvious the dermatitis has begun. There is more dermatitis here, and its spread can be traced from this area. The eruption of atopic dermatitis is more likely to appear at several or many places. Acute, oozing dermatitis of the face is common in atopic dermatitis in infancy, very uncommon in the atopic dermatitis of childhood. If the dermatitis under consideration began on the face in infancy and has persisted either there or on other parts of the body for several years, it is almost certainly atopic. If it began on the face after the age of infancy and is acute with a good deal of edema, it is almost certainly of the contact variety.

I am afraid that the foregoing is a very incomplete, imperfect, and probably, in parts, inaccurate discussion of contact dermatitis in young children, but it is a very much confused subject, and so I crave indulgence. It is a relatively unexplored field which needs a great deal more exploration, and most of the information concerning it at present is woefully vague and inaccurate.

It is plain that most so-called eczema of young children falls into the atopic group and may be due to proteinlike substances in foods or environmental particles, such as various animal danders, pollens, or dusts. There are, however, not a few cases which do not fall into this group. As pediatricians, we are such specialists in diet that we have a tendency to exaggerate its importance. There are too many patients with contact dermatitis treated by removal of milk, eggs, or wheat from the diet. While I by no means agree with those who pay no attention to food sensitization as a cause of eczema, I urge pediatricians to pay more attention to external causes.

3. Fungus Infection.—Eleven cases. (No discussion.)*

4. Seborrheic Dermatitis.—Four cases. (No discussion.)†

5. Nummular Eczema.—Three cases. Nummular eczema is a curious condition, not very uncommon, and is of some importance, for it is usually wrongly diagnosed as atopic dermatitis and treated by removal of foods from the diet without any benefit whatsoever. I have seen it more frequently in the clinic than in private practice. It is not mentioned in some of the modern dermatologic textbooks, nor is there much about it in the periodical literature. Pollitzer[10] discussed it in 1912, and Chipman[11] in a short but excellent paper in 1934. Chipman's paper was discussed by several well-known dermatologists who all agreed that there was such a thing, that it was a distinct clinical entity, and that it should be classified under eczema.‡ The best textbook discussion of it is in Sulzberger's book on *Dermatologic Treatment.*

*See Hill, L. W.: J. A. M. A. 103: 331, 1934.

†See any textbook on dermatology.

‡See also Gross, P.: Arch. Dermat. & Syph. 44: 1060, 1941 (published after this paper was written).

Nummular eczema is characterized by sharply defined circular or oval patches, usually of a rather dark color, from the size of a dime to that of a silver dollar, occurring often on the extensor surfaces of the arms or legs. It may occur on any part of the body, including the face. The small patches are more likely to be more round than the larger ones, which may be sometimes irregular or more oval in shape. The individual patch is composed of innumerable very fine vesicles; the older and larger patches are always thick and boggy, always a little moist but not "weeping." The patches occasionally clear a little in the center but not as much as patches of ringworm do, nor do they on close examination resemble those of seborrheic dermatitis. They are thicker and more moist and usually are of a darker color. They do not suggest psoriasis, though never having seen a case of psoriasis in a baby or very young child I have no very clear idea as to what it should look like at this age. The patches of nummular eczema are more regular in outline than those of atopic dermatitis, there is a sharper line of demarcation between the diseased and healthy skin, the larger ones are more "boggy" and exudative, and there is no lichenification. Itching may be almost absent or moderate; there is never the terrific itching such as in atopic dermatitis. The skin, except for the scanty or numerous circumscribed patches, is smooth and of good quality. The scalp is not involved.

Nothing whatever is known of the etiology of this dermatosis. The most important thing is to remember that it exists and not to misdiagnose it and treat it as atopic dermatitis. As far as is known it has nothing to do with allergy. I have seen no patient with nummular eczema who had positive skin tests. The following is a characteristic example:

J. M., 14-month-old male. Eczema began at the age of 4 months and has persisted in spite of all sorts of local and dietetic treatment. He has been on a diet of goat's milk for the last three weeks. Until recently there had been very little itching; moderate at present.

Examination showed sharply margined, symmetrical patches the size of a silver dollar on both cheeks. Over the extensor surfaces of the arms and upper legs there were five or six patches, some the size of a quarter, some the size of a fifty-cent piece. On the lower legs there were several more irregularly shaped and larger patches, also with sharp margins. Skin tests were negative.

Treatment by me was entirely unsatisfactory. He was then sent to a superfine dermatologist who did no better.

*6. Circumscribed Neurodermatitis.**—Two cases. Circumscribed neurodermatitis does not occur in infants, is rare in young children, fairly common in older children, and common in adults. It consists usually of one, occasionally of two or three, lichenified patches of varying size,

*I have not included under circumscribed neurodermatitis several cases which would be classified under this heading by some authors, as I do not feel that the more or less localized lichenification, which is so common in atopic dermatitis, should be so classed. The patch should possess all the characteristics of this condition as typically seen in adults before it is classified as "circumscribed neurodermatitis."

often on the back of the neck or extremities. The patch is raised a little above the rest of the skin, and the margins are often sharp. It is much thickened, and looks like the skin of a rhinoceros. It is crossed by innumerable fine furrows with raised areas in between (lichenification). It is rarely moist. It might better be called "circumscribed lichenification," and is sometimes so called (lichen planus circumscriptus).

Lichenification is frequently seen in children with atopic dermatitis, particularly in front of the elbows and back of the knees, but does not so often take on the circumscribed character described.

Circumscribed neurodermatitis may develop in allergic or nonallergic individuals. The primary cause is thought to be itching, possibly from atopic dermatitis, possibly from unknown causes, which, followed by continual rubbing and scratching, enables the affected area in predisposed individuals to take on its characteristic appearance and to attain finally, on account of chronic and more or less permanent change in the tissue, a "selbständigheit," as the Germans have said, independent of its primary cause. It is not influenced by immunologic treatment, even in allergic persons.

SUMMARY

Classification is probably more important and certainly more difficult in dermatology than in any other branch of medicine. I have attempted to apply what seems to me an excellent classification, proposed by an outstanding dermatologist, to an actual group of children with eczematoid eruptions in order to determine the relative frequency and criteria for differentiation of the various forms and in order to call the attention of pediatricians to the desirability of classification before attempting etiologic treatment.

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SPONTANEOUS ACIDOSIS IN PREMATURE INFANTS

A Clinical Report

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DISTURBANCES of the acid-base balance of apparently healthy premature infants are rarely mentioned. In 1937 one of the authors (A. McB.) found that the plasma carbon dioxide combining power was low in several premature infants who were more than 1 week of age and whose only abnormal signs were sluggish nursing, with failure to gain weight, and some difficulty in breathing, which was interpreted as hyperpnea. Since that time the carbon dioxide combining power was determined in all premature infants who had one or more of these findings.

The following is a typical case history of one of these infants (A-29831):

The mother, a 19-year-old primipara, was given adequate syphilitic treatment. The infant's birth weight was 2,000 Gm. On the ninth and thirteenth days of life the infant appeared dehydrated and received subcutaneous infusions of physiologic saline. During the third week of life he gained poorly and required gavage feedings, and on the twenty-first day of life he displayed rapid, shallow respirations. The carbon dioxide combining power of his blood plasma was 21 volumes per cent. He was given 75 c.c. of M/6 sodium lactate on the twenty-first day. He gained 335 Gm. in weight during the next forty-eight hours, began to nurse well, and a second carbon dioxide combining power was 52 volumes per cent. Subcutaneous saline was given twice during the following week and three times during the fifth week of life. The hemoglobin content of the blood was 61 per cent on the twenty-ninth day. He received 50 c.c. of citrated blood on the thirty-eighth day of life and was discharged on the forty-ninth day in good condition, weighing 3,210 Gm.

While premature infants generally are considered to have a more labile acid-base equilibrium than those who are full term, we can find no report of low carbon dioxide combining power determinations in premature infants who have become spontaneously acidotic. None of these infants had vomiting or diarrhea, and we have discovered no precipitating factor. The urine of each infant has been negative to qualitative tests for ketone bodies.

Marples and Lippard[1] have demonstrated that cow's milk contains 12.85 milliequivalents of base per 100 c.c. For acid-base regulation, 6.98 milliequivalents may be virtually ignored since they are made of calcium and magnesium,* leaving approximately 5.87 milliequivalents of fixed base per 100 c.c. of whole milk formula to neutralize acid radicals for storage and excretion. Gordon and his co-workers[2] have shown that

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*Analyses of formulas given at Duke Hospital are in close agreement with these figures.

TABLE I

SPONTANEOUS ACIDOSIS IN PREMATURE INFANTS

A SUMMARY OF CASES

CASE NO.	BIRTH WEIGHT (GM.)	AGE WHEN ACIDOTIC (DAYS)	WEIGHT WHEN ACIDOTIC (GM.)	SYMPTOMS	PLASMA CO_2 COMBINING POWER (VOL. PER CENT)	FEEDING	C.C. OF M/6 SODIUM LACTATE	COMMENTS
92149	1,770	25			22	L.A.E.M.* + 7½% c.s.	60	
		36	1,900		19		110	
		50		Hyperpnea	18		125	
		51		Hyperpnea	34			Discharged as well on eighty-eighth day
A1037	2,120	22	2,165	Abdominal distention; hyperpnea	16	Olac†	120	N.P.N., 70 mg. per 100 c.c.; gained 235 Gm. in forty-eight hours; recovered promptly
A2149	2,300	5	2,290	Sluggishness	29	L.A.E.M. + 7½% c.s.	60	No further difficulty
A17802	1,700	41	2,580	Hyperpnea	25	L.A.E.M. + 7½% c.s.	70	Recurrence on fifty-fifth day
A19269	2,470	24	2,700	Hyperpnea	31	L.A.E.M. + 7½% c.s.	80	N.P.N., 54 mg. per 100 c.c. of blood
A29831	2,000	21	1,975	Hyperpnea	21	L.A.E.M. + 7½% c.s.	150	Recovered promptly
A32238	2,230	22	2,590	Sluggish; nursed poorly	22	L.A.E.M. + 7½% c.s.	120	Recovered; no recurrence
A33192	1,435	17	1,570	Hyperpnea	32	L.A.E.M. + 7½% c.s.		50 c.c. physiologic saline subcutaneously; required frequent subcutaneous fluid before seventeenth day
		40	2,610	Hyperpnea	35		60	
A33884	2,160	21	2,220	Hyperpnea	22	L.A.E.M. + 7½% c.s.	70	
		31	2,660	Hyperpnea	20		90	Recovered
A34615	1,800	19	1,980	Poor feeding	19	L.A.E.M. + 7½% c.s.	120	No recurrence

A35670	1,825	12	1,920	Hyperpnea	16	L.A.E.M. + 7½% c.s.	116	Lactic acid removed from formula after first attack of acidosis without benefit; molar Na-lactate 10 c.c. by mouth daily from twenty-eighth to thirty-seventh day; no diarrhea or fever throughout course
		19	2,270	Hyperpnea	19	Evap. milk plus 7½%	120	
		26	2,580	Hyperpnea	21	c.s.	150	
		37	2,940	Hyperpnea	38		60	
		39	3,060	Hyperpnea	22		160	
		45	3,470	Hyperpnea	34		110	
		52	3,500	Hyperpnea	33		125	
		59	3,770	Hyperpnea	21		120	
		70		Hyperpnea	39		-	
		77		Hyperpnea	32		120	
		81	4,020	None	47		-	
A37449	1,785	31	2,300	None	23	L.A.E.M. + 7½% c.s.	120	Had frequent dehydration requiring subcutaneous saline infusions
A43598	1,425	28	1,800	None	24	L.A.E.M. + 7½% c.s.	35	Frequently dehydrated; expired on forty-fourth day; no autopsy
		38	1,960	Hyperpnea	23		40	
		42		Hyperpnea	28		50	
A44733	1,275	32	1,400	Hyperpnea	32	Various formulas	30	Feeding problem; formulas used: olac, evap. milk + lactic acid + cane sugar; autopsy findings negative
		36	1,440	Hyperpnea	33		30	
		37		Hyperpnea + abdominal distention			25	
		59			35		60	
		62	2,160		21		50	
		64			Expired		-	
A46353	1,675	15	1,680	Hyperpnea	29	L.A.E.M. + 7½% c.s.	50	No recurrence; discharged as well
		21	2,040		36		38	
		40	2,625		26		105	
A46383	1,725	28	2,280	Hyperpnea	39	Olac	60	Rapid weight gain maintained after therapy; discharged as well
		49	3,260		32		120	
A52425	1,770	46	2,810	Hyperpnea	33	L.A.E.M. + 7½% c.s.	60	Recovered
A52454	2,235	13	2,180	Hyperpnea	22	Breast + L.A.E.M. +	50	Recovered
		14	2,360	Hyperpnea	29	7½% c.s.	140	
A52808	2,200	23	2,450	Hyperpnea	33	Breast	75	Gained 310 Gm. in forty-eight hours; recovered

*L.A.E.M. + 7½% c.s. = equal parts of evaporated milk and water with the addition of 0.75 per cent lactic acid and 7.5 per cent cane sugar.
†Olac = 1 part of olac and 6 parts of water under 2 weeks of age; 1 part of olac and 4 parts of water after 2 weeks of age.

TABLE I—CONT'D

CASE NO.	BIRTH WEIGHT (GM.)	AGE WHEN ACIDOTIC (DAYS)	WEIGHT WHEN ACIDOTIC (GM.)	SYMPTOMS	PLASMA CO_2 COMBINING POWER (VOL. PER CENT)	FEEDING	C.C. OF M/6 SODIUM LACTATE	COMMENTS
A54967	2,040	15	2,300	Hyperpnea	31	L.A.E.M. + 7½% c.s.	60	Recovered
		16	2,450	Hyperpnea	21		130	
A55409	2,075	17	2,385	Irregular resp.	27	Olac	120	Weight gain out of proportion to fluid received
		19	2,560	None	45		-	
A57158	2,250	9	2,060	Hyperpnea	35	L.A.E.M. + 7½% c.s.	120	
		51	3,360	Hyperpnea and	15		200	
		65	3,850	distention and poor appetite	33		90	Recovered
A58637	1,800	16	2,370	Hyperpnea	18	L.A.E.M. + 7½% c.s.	220	Received molar Na-lactate by mouth, 5 c.c. t.i.d. after forty-second day; gained rapidly
		19	2,500	Hyperpnea	18		150	
		33	2,840	Hyperpnea	28		90	
		36	2,980	Hyperpnea	32		60	
A60133	1,515	58	2,670	Irregular resp.	20	L.A.E.M. + 7½% c.s.	50	Hemoglobin, 63 per cent; transfused; recovered
		59	2,850	Irregular resp.	35		120	
A60961	1,575	23	2,000	Dyspnea and ir-	32	L.A.E.M. + 7½% c.s.	-	Molar Na-lactate 5 c.c. t.i.d. twenty-fifth to fortieth day
		41	2,720	regular breath-	32		120	
		42	2,640	ing	35		120	
A65098	1,785	19	1,800	Cheyne-Stokes respiration; ashen color	31	Olac	120	Fever 39.5° C. (R) spike; returned to normal promptly after therapy; no recurrence; rapid weight gain maintained

for an average daily weight gain of 35.6 Gm., their premature infant retained 3.8 milliequivalents of fixed base per twenty-four hours from their diet. It is obvious that on such intake the acid-base equilibrium of a premature infant is regulated on a narrow margin, especially if one considers that the urinary excretion is near the physiologic limits of acidity. Aside from inorganic acid excretion, the organic acid output of the thriving premature is from two to five times that of full-term infants, and the organic with corresponding reduction plasma in bicarbonate.[3]

Acidosis in the premature is therefore a matter of degree, and the diagnosis rests upon clinical as well as chemical findings. Hyperpnea is not always present, and in certain infants no signs other than sluggish reactions to stimuli, poor nursing, failure to gain weight, or other signs of "poor condition" without apparent cause were present. Several infants had sudden rises of temperature, without evidence of infection, which subsided promptly after administration of sodium lactate. Several premature infants who had mild diarrhea after the recognition of the acidosis were omitted from this series since diarrhea so often results in acidosis, even though here it seemed to be a secondary factor. We feel that plasma carbon dioxide combining power of 35 volumes per cent is the lower limit of normal in premature infants.

Administration of sodium lactate solution subcutaneously seems to be more efficient than intravenous administration since as much as 90 per cent of the salt may be excreted by the kidneys unmetabolized when given intravenously. However, we found that giving the calculated dosage of 60 c.c. M/6 sodium lactate per kilogram of body weight, one-third by vein and two-thirds subcutaneously, was satisfactory.

Comparison of the rate of the gain in weight for three days before and after the administration of sodium lactate solution to the infants in this series shows the rate of weight gain to be almost doubled afterward and the gain is maintained. Premature infants who repeatedly show signs of dehydration and require frequent subcutaneous infusions of saline respond in like manner when sodium lactate solution is given and the tendency toward dehydration is curbed. We feel, therefore, that dehydration even without signs of acidosis is significant of base deficit. In addition, there is prompt appearance after therapy of a good cry, vigorous nursing, and the other signs of a thriving infant.

CONCLUSIONS

1. A group of twenty-six premature infants, who had low plasma carbon dioxide combining power, is presented.

2. Twenty-one infants had hyperpnea or difficult breathing, and five patients had no signs specific for acidosis.

3. Administration of sixth molar sodium lactate solution resulted in the rapid disappearance of signs.

4. No precipitating factor has been determined.

5. All premature infants who are not thriving or who have hyperpnea, dehydration, or weight loss, or who fail to gain properly should be studied routinely for acidosis or inadequate base intake.

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THE PATHOGENESIS OF CHOREA

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INTRODUCTION

ALTHOUGH Sydenham's[51, 52] classical description of chorea was published in 1685, the pathogenesis of the disease has remained an unsolved problem. With new conceptions of nervous activity and with modern methods of anatomic and physiologic investigation of the nervous system, an attempt may be made to understand some of the factors responsible for the choreic phenomena.

The choreas of childhood largely are composed of what is now almost universally designated as rheumatic chorea and the rarer congenital chorea. The irregular movements, however, are essentially the same in both. Congenital chorea as a pure clinical entity is not accompanied by spasticity in any limb or by athetosis. The irregular movements are present both at rest and with voluntary activity. Congenital chorea is present from early infancy and varies little in degree or range with advancing maturity. A child with congenital chorea is able almost always to perform successfully such complicated voluntary acts as writing and drawing. Apparently the same type of functional adjustment to irregular movement is developed as with congenital nystagmus. Indeed one of the quickest methods of distinguishing congenital chorea from rheumatic chorea is to ask the patient to write his name. With the former defect the result is legible but with the latter it is almost completely indecipherable.

THE PATHOLOGY OF CHOREA

History.—Richard Bright[7] was probably the first to suggest that chorea and rheumatic heart disease were related etiologically. From his pathologic studies he concluded in 1831, "We also see that rheumatism is so intimately connected with chorea that in some cases it seems to have been an exciting cause, at other times to be but a concomitant." In 1843, Todd,[54] supporting this idea, said, "It often occurs in the rheumatic diathesis, as I believe is indicated by the frequent coexistence of chronic valvular disease of the heart with it; and it frequently comes on after attacks of rheumatic fever." He also was the first definitely to state that he believed chorea to be a disease of the brain with the site of affection in the mesencephalon.

Sée[50] in 1850 wrote the first monograph on chorea. He agreed that it was part of a rheumatic infection and that it involved the nervous system, but he did not suggest any site of election in the brain.

From the University of Chicago.
Presented before the American Neurological Association, June 9, 1941.

In 1869, Kirkes[28] supported this general theory and is quoted as saying that "embolic particles are carried from the heart to the spine and there set up the irritation which is productive of chorea." Wilkes[63] denied this theory and maintained that "chorea like epilepsy is due to a disturbance of the whole of the centers."

Jackson,[27] in 1869, described the brain of a young man who died as a result of chorea. "I found slight extravasations in several parts of the brain, chiefly on the surface, and by the microscope, I discovered within numerous small arteries much granular matter. Although the movements in this patient's case were almost limited to one side, yet I found the appearance of blocking in the region of each middle cerebral artery. I found similar changes in other parts of the brain."

Broadbent[8] considered chorea to be a symptom and not a disease, and he believed that the site of affection in the brain was of importance and not the mode of injury. He described chorea as a "delirium of the sensori-motor ganglia."

Bastian[4] concluded that chorea was effected in an individual of a certain age and nervous temperament by a disturbed nutrition in the corpora striata and adjacent parts of the brain due to multiple minute thromboses.

Raymond[45] reviewed the reports of fifty-eight fatal cases of chorea. He reported that thirty-nine of them were said to have round cell infiltration in the brain.

Westphal, Wassermann, and Malkoff[62] and later Poynton and Holmes[44] reported finding a streptococcus in the blood and in the brain of patients with chorea. Mircoli[39] found a staphylococcus in the brains of fourteen of seventeen patients with acute chorea.

Turner[57] described changes in shape and structure of the large pyramidal cells in the motor cortex in five cases of chorea. Only this area of the brain was examined.

Thomson[53] reported swelling of the ganglion cells of the brain with changes in their staining reactions. He found no alterations in the blood vessels of the nervous system. He concluded that chorea was due to a toxin circulating in the blood.

Rheinhold[47] reported pial bleeding, and thrombosis of the superior longitudinal transverse and petrosal sinuses in a young woman who died with acute chorea and chlorosis.

Abrahams[1] described toxic changes in the cortical cells and infiltration of the perivascular spaces in a fatal case of chorea of pregnancy. He concluded that the signs of inflammation in the brain were the result of toxic alterations in the blood.

In two fatal cases of acute chorea Reichardt[46] found hyperemia of the cerebral cortex and perivascular infiltration but no changes in the structure of the ganglion cells of the cortex.

West[61] and later Kopczynski[29] both reported that they could find no pathologic changes in the brain in chorea.

Dupré and Camus[14] described meningeal congestion, cellular infiltration of the cortex, and cellular pallor.

Delcourt and Sand[13] found that the meninges were infiltrated with inflammatory cells and that the meningeal vessels were widely dilated. The cerebral cortex was hyperemic, edematous, and in places necrotic. The nerve cells were markedly altered in the cerebral cortex and in the basal ganglia.

Fiore[17] reported, in two cases of acute chorea in children, evidence of neuronal degeneration, hyperemia, and diffuse inflammation of the cerebral cortex.

Marie and Trétiakoff[36] described evidence of acute cellular infiltration of the meninges and small scattered inflammatory nodules in the cerebral cortex and in the basal ganglia.

Greenfield and Wolfsohn[24] described neuronophagia in the cells of the cerebral cortex and the basal ganglia of a 7-year-old boy who suffered from acute rheumatic chorea.

Lhermitte and Pagniez[33] described diffuse cellular degeneration in the cerebral cortex, the putamen, and dentate nucleus of a girl 19 years old who died with acute chorea.

Lewy[32] published a monograph on the pathology of choreas. He described the changes as being mainly the destruction of the ganglion cells with some perivascular infiltration. He found only one patient with emboli in the cortical vessels. The cellular changes were not only in the basal ganglia but also in the deeper granular layers of the cortex.

Van Gehuchten[21] made a very detailed study of the brain of a 15-year-old boy who died with acute chorea. The brain was markedly congested. There were small hemorrhages in the posterior part of the putamen, the caudate nucleus, and the thalamus and irregularly placed in the cerebral cortex. Cellular degeneration was present in the brain stem, in the thalamus, in the basal ganglia, and in the dentate nucleus of the cerebellum. In the temporal, occipital, and parietal regions of the cortex there was little damage, but cellular degeneration was marked in the frontal regions.

Laederich, Mamou, Beauchesne and Vaisman[30] reported the autopsy of a woman who died with acute chorea. The brain was studied by Levaditi, and he reported intense dilatation of the vessels in the cerebral cortex. There were also perivascular cuffing and neuronal destruction and in the white matter numerous small hemorrhages.

Ziegler[66] described chromatolysis and neuronophagia in the cells of all parts of the brain and spinal cord of a girl who died with acute chorea.

Von Santha[49] published a very comprehensive study of the brain of a 15-year-old girl who died with chorea. Few inflammatory cells were present in the pia mater but many small pial vessels were thrombosed and recanalized. As a result of such vascular changes, numerous areas of incomplete softening were found in the cerebral cortex, particularly

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in the precentral gyrus and the temporal region. There were no cellular changes in the basal ganglia, the thalamus, the mesencephalon, or the brain stem. A few scattered areas of damage were present in the dentate nucleus.

Urechia[58] described perivascular infiltration in the basal ganglia and slight cellular degeneration in the cerebral cortex, the cerebellum, and the brain stem, in the brain of a 17-year-old girl who died with acute chorea.

Babonneix and Lhermitte[3] reviewed the pathologic study of the brain of a child who died as a result of acute chorea, which study had previously been reported by Mery and Babonneix. They found cellular degeneration, which was most marked in the motor cortex and in the basal ganglia, but no evidence of perivascular cuffing in any region.

Callewaert[10] studied the brain of a 15-year-old girl who had died as a result of acute chorea. He found cellular degeneration in the cerebral cortex of the central sulci, in the caudate nucleus and putamen, and in the thalamus.

A review of the neuropathologic changes in the brains of patients suffering from chorea reveals a considerable diversity of findings. In the acute cases the most common abnormality is evidence of neuronal degeneration manifested by swelling of the cell, tigrolysis, eccentricity of the nucleus, neuronophagia with or without vascular changes. These findings are pronounced in the cerebral cortex, the basal ganglia, and cerebellum. They are not, however, pathognomonic of chorea and are found in many other toxic or infective conditions which have no choreic manifestations. In other cases, vascular changes, such as proliferation, thrombosis, or hemorrhage, are pronounced in the cerebral cortex, basal ganglia, or cerebellum. These pronounced alterations may be associated with any or all of the neuronal degenerative changes mentioned. They, too, are not pathognomonic of chorea, being found frequently in other conditions.

CASE REPORTS

We have had the privilege of examining the brains of two patients who died while suffering from acute rheumatic chorea.

CASE 1.—M. N. was a 13-year-old girl who was born prematurely. Her development was slow. She did not sit up until 15 months of age and did not walk until 2 years of age. At the age of 12 years she was able to dress and feed herself but could not play ball or roller skate. Her school work was of average quality. When first examined at that age she had ataxia of the left arm and left hand. There were twitching movements of the neck muscles, especially of the left sternomastoid, which rotated the chin toward the right shoulder. A diagnosis of dystonia was made.

She was admitted to the Children's Memorial Hospital in Chicago on April 8, 1937, because of frequent purposeless movements of the face, arms, and legs, which had appeared a few days before admission. At that time she had an apical systolic

murmur. The spinal fluid contained 50 lymphocytes. Her temperature was 101° F. She died with a high fever on April 19, 1937. The clinical diagnosis was Sydenham's chorea superimposed upon a dystonia.

A complete post-mortem examination was made. The heart weighed 180 Gm. The myocardium of the left ventricle revealed areas of scarring and vegetations on the borders of a stenotic mitral valve. The tricuspid valve was dilated. There were passive congestion in the lung and a small calcified nodule in the posterior aspect of the left upper lobe.

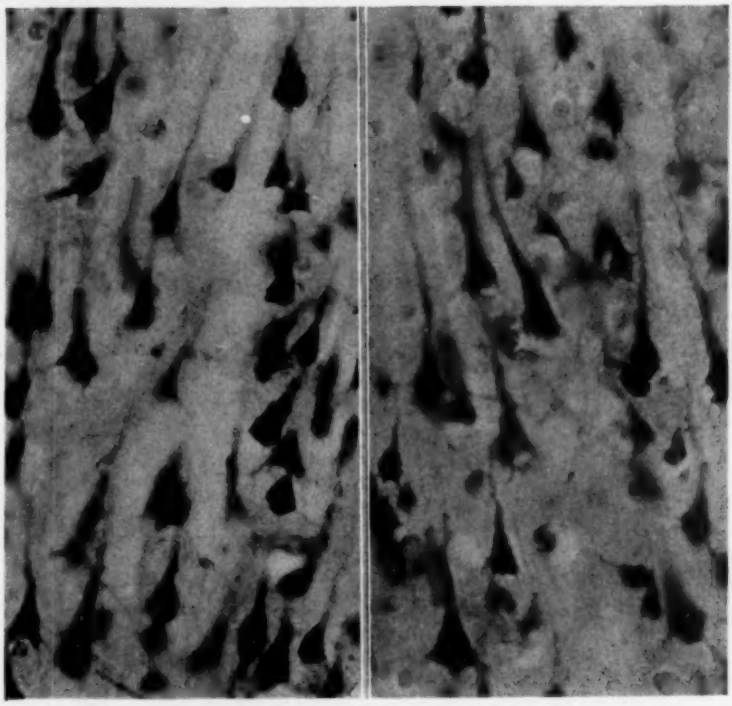

Fig. 1.—Case 1. Photomicrographs of the cells of the third layer of the premotor cortex, showing the neuronal changes. The cell cytoplasm is diffusely stained and the cell processes are irregular. Many of the nuclei are so densely stained that the nucleolus cannot be seen. Nissl stain ×360.

Examination of the Nervous System.—The dura mater appeared normal. The brain weighed 1,230 Gm. The cerebral hemispheres were well developed, and the fissural arrangement was not abnormal. The convolutions were full. Neither the brain stem nor cerebellum presented gross abnormalities. A midsagittal section revealed no ventricular dilatation and no abnormality of the midline structures except the absence of the massa intermedia.

The left thalamus and striatum were sectioned serially and every twenty-fifth section stained by Nissl's method. Representative blocks were taken for cell and myelin stains from the cerebellar vermis and hemispheres, the medulla, pons, mesencephalon, hypothalamus, right thalamus, and right caudate nucleus and numerous blocks from the cerebral cortex of all lobes, including four from the right central region.

The cytoarchitecture of the various parts of the brain appeared normal except for the precentral convolution. In this gyrus, where normally the Betz cells are so prominent, the cytoarchitecture was similar to that of area 6, and there were no gigantopyramidal cells. The precentral agranular cortex abutted normal postcentral granular cortex and anteriorly continued as the cortex of area 6.

There were marked neuronal changes in the cells of the cerebral cortex, especially in those of the third layer. Most of the neurones were slightly swollen, and there was a clear space around many of them. The cytoplasm of the cell stained diffusely so that the nucleus was recognizable only with difficulty. The nucleolus was darkly stained. Many vacuoles were present in the cytoplasm of the neurones. Many of the cell processes were corkscrew and irregular in shape (Fig. 1). All the blood vessels were distended, but there was no evidence of perivascular infiltration or proliferation.

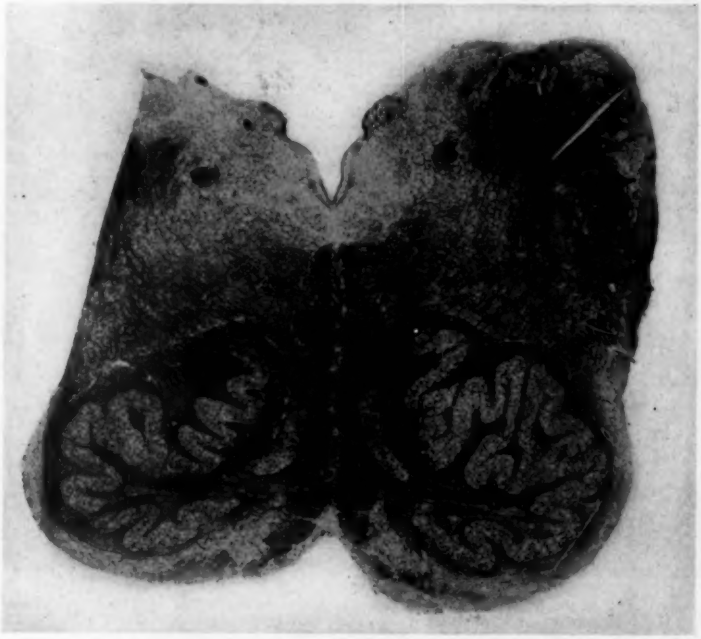

Fig. 2.—Case 1. Photomicrograph of the medulla to show the almost complete absence of the pyramids. Smith-Quigley technique ×8.

These neuronal changes were seen in all parts of the cerebral cortex, although they were pronounced in sections taken from the central regions.

The cerebellum appeared to be normal cytoarchitecturally. The molecular and granular layers were well developed. The Purkinje cells were numerous. The cells of the dentate nucleus stained poorly but were otherwise normal.

The pontine region had a normal structural appearance, except for a marked decrease in the longitudinal fasciculi of the pons. The cells of the pontine nuclei stained fairly well. The medulla oblongata was well developed except for the pyramids which were very small. The cells of the inferior olive were slightly swollen and rounded (Fig. 2).

The mesencephalon contained normal-appearing neurones except for a few near the locus caeruleus which appeared to be undergoing tigrolysis. The neurones

of the caudate nucleus and thalamus were pale and were swollen. The hypothalamic nuclei appeared normal except for an intense staining of some of the cells.

Discussion.—This case of dystonia with superimposed Sydenham's chorea is of great interest due to the absence of Betz cells and the virtual lack of the pyramidal tracts. In spite of this deficiency the child appeared to be able to carry out almost normal movements with the upper and lower extremities. This is, of course, not unexpected in view of the studies of Tower[55] on monkeys after section of the pyramids. The development of chorea in this case would appear to negate Wilson's theory[64] as to the pathogenesis of the condition. He emphasizes the necessity of an intact or practically intact pyramidal tract for the movements to appear. However, so long as there is a functioning pathway from the cerebral cortex to the spinal cord there is no reason why such involuntary movements should not occur.

CASE 2.—R. B., a 6-year-old boy, was admitted to the University of Chicago Clinics on March 10, 1936, with the history that he had been jerky and nervous for two weeks. He was the only child in the family. His birth was normal and his early development had been marred by no serious illness or accident.

He presented typical choreiform movements of hands and arms. His speech was slurred. The deep reflexes were reduced, but there were no pathologic reflexes. His heart was not enlarged, but there was a harsh apical systolic murmur. Subcutaneous nodules could be palpated in his scalp in the occipital region.

For six weeks he was kept in bed and given phenobarbital and salicylates. At the time of his discharge from the hospital he had almost completely recovered. His illness recurred in July, 1936, but by September, 1936, he was quite well.

In May, 1937, his tonsils were removed, and during that month he again had evidence of chorea. The signs were most marked in the left hand and in the left arm.

He was not seen again until May, 1939, but was said to have been well in the interval. Then he was admitted to the hospital with signs of active chorea, which had been present for three weeks. His heart was 65 per cent oversize. There was evidence of a partial auriculoventricular block and myocarditis on electrocardiographic studies of his heart.

He was very listless and weak. His limbs were hypotonic. There were no abnormal reflexes, but the deep reflexes were all reduced. There was a flaccid choreic palsy of the right arm and the right leg, and the voluntary power of the left arm and the left leg was much reduced. Although he remained in bed, cardiac decompensation developed and edema appeared in his face and in his legs. Despite appropriate treatment the circulatory failure advanced and he expired on June 2, 1939.

A blood culture taken a week before his death was negative for all organisms.

A complete post-mortem examination made by Dr. E. M. Humphreys disclosed rheumatic verrucous mitral and aortic myocarditis, mural endocarditis with many active and involuting Aschoff bodies, extreme fatty degeneration of the myocardium, cardiac dilatation with marked dilatation of the mitral orifice and moderate enlargement of the tricuspid opening, focal proliferative lesions of the blood vessels of the brain, lungs, kidneys and liver, endothelial hyperplasia, disseminated thrombosis of blood capillaries, terminal streptococcal septicemia, infected infarct of the right lung with regional bronchopneumonia and fibrinous pleuritis, disseminated lobular hemorrhages in both lungs, moderately advanced pulmonary passive hyperemia and edema, chronic bronchitis, focal proliferative glomerulitis and marked

parenchymatous degeneration of the kidneys, focal fibrous hepatitis, marked hepatic passive hyperemia and fatty changes, focal atrophy and focal waxy degeneration of skeletal muscles, edema of the extremities, face, and eyelids, slight ascites and purplish mottling of the skin.

Examination of the Nervous System.—The brain weighed 1,275 Gm. The dura mater appeared normal and the dural sinuses were patent. The cerebral hemispheres were symmetrical and well developed. The convolutions of the central regions were somewhat narrow on both sides but especially on the left side. The sulci were correspondingly enlarged. The leptomeninges were translucent and thickened on the convexity of the hemispheres. The cerebellum and brain stem appeared normal. Serial coronal sections of the cerebral hemispheres and brain stem revealed no gross abnormality. The ventricular system was not dilated.

Representative blocks were taken from the frontal and occipital poles and the posterior parietal region. Four blocks were taken from the central gyri, one from each of the face, arm, trunk, and leg areas. The basal ganglia (caudate nucleus, putamen, globus pallidus, and thalamus), along with the adjacent cortex of the frontal and temporal lobes, brain stem and cerebellum were sectioned serially.

Every twenty-fifth section was stained by Nissl's technique and the adjacent section by the Smith-Quigley technique for myelin. Sections from the blocks of cortex were stained both for cells and myelin by these methods. In addition, appropriate sections were impregnated by Perdrau's method and others stained for elastic tissue.

The pia arachnoid across the sulci of the cerebral cortex was markedly thickened, although it did not contain an abnormal number of cells within its meshes (Fig. 3). The thickening was largely composed of fine, loosely arranged reticulin. The outer layer of the arachnoid membrane in places was quite cellular and consisted of two or three compact layers of lanceolate cells. The large vessels within the subarachnoid space had small nodular intimal proliferations which projected into the lumen of the vessels (Fig. 4). In places these nodules had split the elastic layer into several strands and in places had so infiltrated it that it could not be recognized. None of these nodular intimal thickenings were of sufficient magnitude to cause an occlusion of the vessel. The nodules exhibited no evidence of degeneration, and there was no cellular infiltration of any of the layers of the vessel wall.

The general cyto- and myeloarchitecture of the cerebral cortex was well preserved throughout the entire extent of the cerebral hemispheres. The neurones of the cortical layers in general stained well and exhibited no serious alterations. Some, however, were stained pale and others rather diffuse. Occasionally small areas of softening or localized atrophy were seen in the cortex (Fig. 5). These usually were present about small thickened blood vessels, which were seen throughout the brain, especially in the cerebral cortex, and involved a circular or oval area with a diameter equivalent to the width of the third layer of the cerebral cortex (Fig. 6). With the exception of the central region of both hemispheres, these lesions were rarely seen. But along the central sulcus, especially in the motor and premotor cortex, these small softenings were numerous. Some were acute, with only a few pale staining neuronal cells remaining in the lesion. Others contained a small amount of blood pigment and an increase in neuroglial elements. Still older ones showed a connective tissue scarring and capillary proliferation in the involved area. Such lesions were almost entirely confined to the gray matter and rarely occurred in the white matter. They were particularly numerous in the arm areas of the central cortex and less numerous in the face and leg areas. They occurred somewhat more frequently in the left than in the right arm area. The neurones adjacent to these lesions showed varying cellular alterations.

The small vessels of the cerebral cortex were thickened and the intima markedly proliferated, so that the lumen of the vessel was divided by one or more

septa into compartments (Fig. 5*B*). This marked proliferation was sufficient to cause an occlusion of some of the cortical vessels, thus producing the softenings previously described.

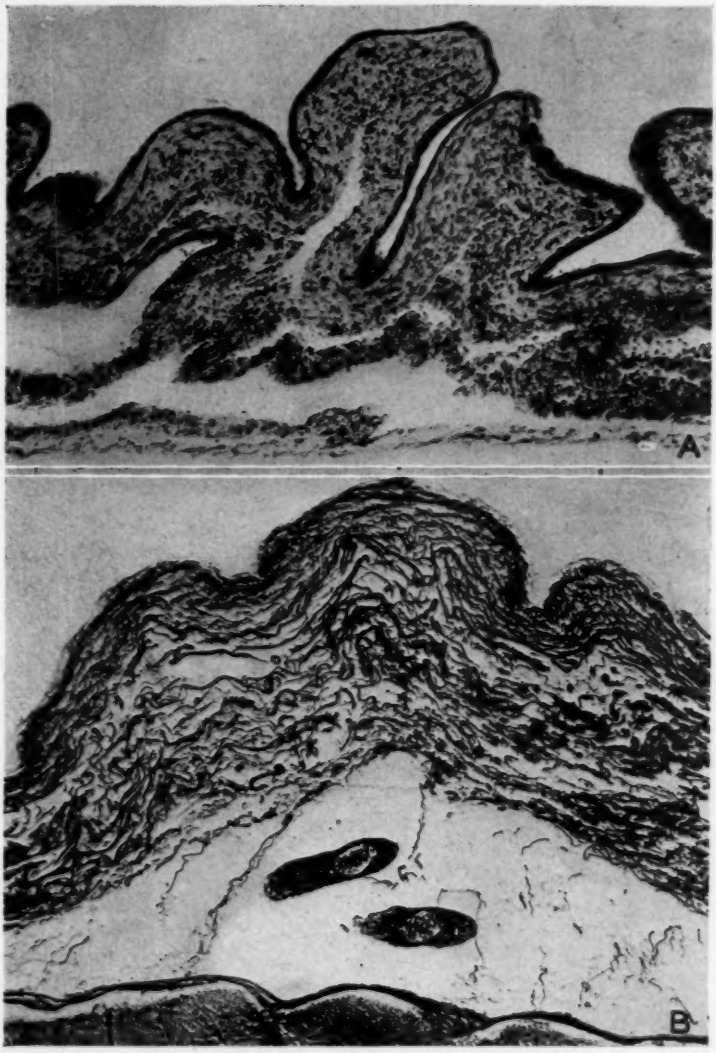

Fig. 3.—Case 2. Photomicrographs of the pia-arachnoid over the cerebral cortex. *A*, Hematoxylin and eosin stain; *B*, Perdrau impregnation to show the reticulin ×105.

The basal ganglia exhibited no significant abnormality. The cells of the caudate nucleus and the putamen appeared essentially normal. Both the large and small cells of the globus pallidus were present in normal numbers and stained well. The

myelinated fibers giving rise to the typical myeloarchitectural picture of the striatum stained well in myelin preparations. The ansa lenticularis was normal. The thalamus and hypothalamus were also unchanged.

The subthalamic body of Luys was well developed and the cells stained well. The substantia nigra did not appear to have quite as many cells as is usual and the

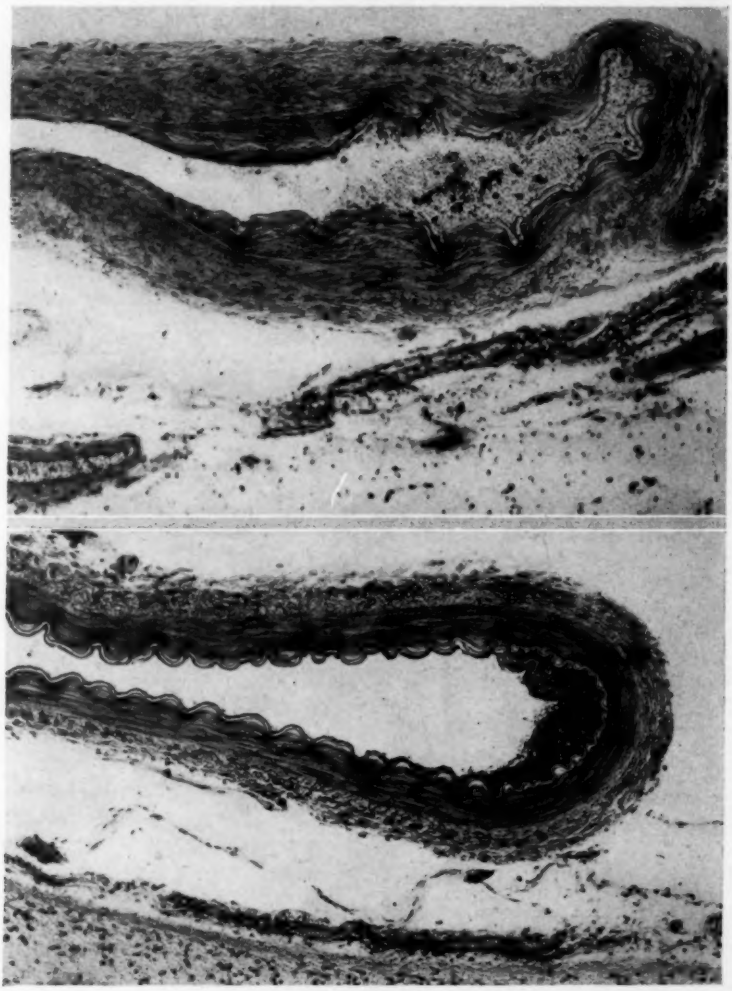

Fig. 4.—Case 2. Photomicrographs of the middle cerebral artery, showing nodular proliferation of the intima and splitting of the elastica. Thionin ×105.

pigment within the cells was less in amount than seen in some cases. There were, however, no perivascular infiltrations or glial nodules, so that these peculiarities were probably within the range of normal variation.

The cerebellar cortex was well developed. The molecular layer presented no abnormalities. The Purkinje cells were normal in number and structure. The granular layer was dense and of normal width. The dentate nucleus was composed of a normal number of cells but the neurones stained more intensely than usually so that the cells appeared angular and the nucleus was hardly distinguish-

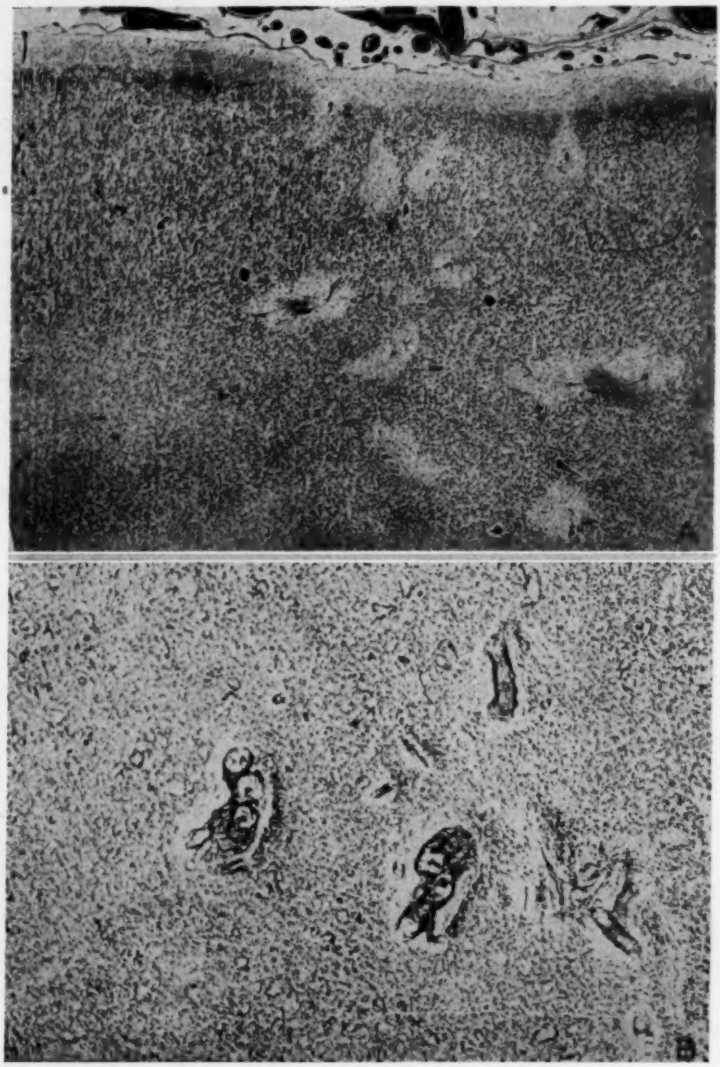

Fig. 5.—Case 2. Photomicrographs of the cortex of the precentral area showing *A*, numerous areas of incomplete softening, each surrounding a small thrombosed vessel (Thionin ×15), and *B*, proliferated blood vessels, showing double and triple canalization (Perdrau ×120).

able from the cytoplasm of the cell. Sections stained for myelin, however, showed no abnormality. The neurones of the inferior olivary nucleus also stained more intensely than normal but otherwise exhibited no abnormality.

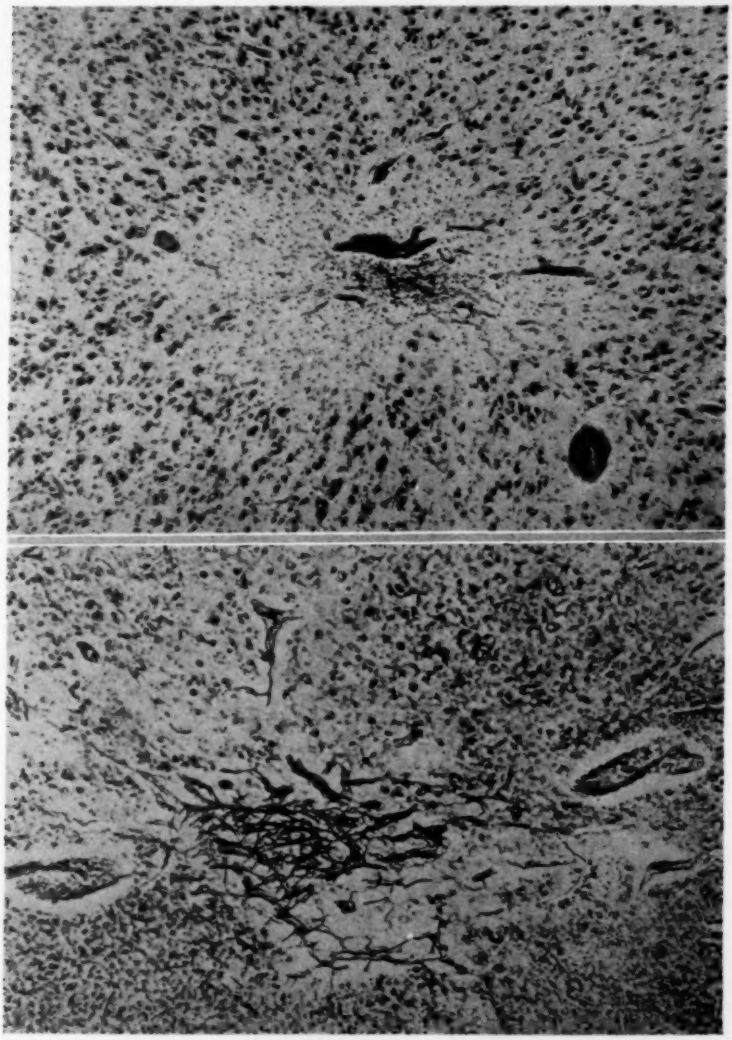

Fig. 6.—Case 2. A higher power photomicrograph of one of the areas of incomplete softening. *A*, Thionin stain (×62); *B*, Perdrau impregnation (×135).

The pons and medulla exhibited no significant abnormality in either Nissl-stained or myelin-stained sections.

Discussion.—The vascular changes in this uncomplicated example of Sydenham's chorea are the most striking pathologic features of this case. Similar alterations were present in many organs of the body as well as in the brain. The pronounced intimal proliferation of the medium-sized vessels giving rise to nodular elevations on the vessel wall are a frequent finding in all organs of the body in rheumatic fever. The severe endothelial proliferation of the capillaries in the brain substance frequently producing an occlusion of the lumen and commonly subdividing the lumen into two or three channels has been described by Glahn and Pappenheim[23] as a specific lesion of rheumatism. They found such lesions in the peripheral blood vessels in ten of forty-seven cases examined. They maintain that this lesion is not the result of recanalization of a thrombotic vessel but the result of active endothelial proliferation.

THE ELECTROENCEPHALOGRAM IN CHOREA

The most striking and most constant characteristic found in the electroencephalogram in chorea is an irregularity of the cortical potentials. In Sydenham's chorea there is a moderate increase of potentials and an increased irregularity of the electrical activity. These disturbances vary in duration from 0.08 to 1 second. It is rare for such disturbances to follow each other with such regularity of spacing or timing that they can be called waves. The irregularity is present in records from all parts of the scalp, but in patients with hemichorea the activity is usually much greater in records made from leads placed on the scalp on the side opposite the movements. The alpha wave is usually present and of normal frequency, although occasionally fragmented and disturbed by this irregular activity (Fig. 7).

In congenital chorea, the cortical activity is increased, but the activity is usually more regular than seen in Sydenham's chorea and delta waves are prominent (Fig. 8).

In some of these electroencephalograms the electrical phenomena are similar to those seen with idiopathic convulsions. That these conditions are not unrelated is well known. One of our choreic patients whose electroencephalogram resembled that seen in the convulsive state subsequently developed epileptic seizures.

It is not always easy to distinguish chorea from convulsions by the electroencephalogram, for some patients with convulsions have much irregular electrical activity in the cortex. In general, the two can be differentiated by the disorganization and irregularity seen in chorea in contrast to the well-organized wave trains commonly at 3 and 6 per second, the slowed alpha wave of approximately 7 per second, and the peculiar and characteristic figures which are often seen with idiopathic convulsions.

These results are substantially in agreement with those reported by Usher and Jasper.[59] They found in twenty-three children with rheu-

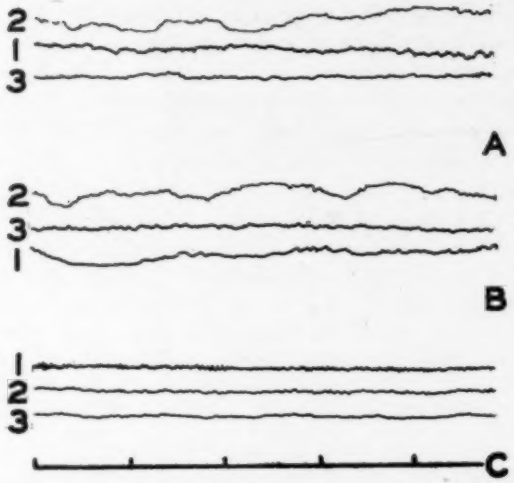

Fig. 7.—Electroencephalograms of a patient suffering from Sydenham's hemichorea. *A* and *B*, taken during the acute attack; *C*, taken six months later when the choreiform movements had entirely ceased. The leads are as follows: *1*, Right frontal to vertex; *2*, right parietal to vertex; *3*, left frontal to vertex.

The abnormal irregular activity and delta waves having a frequency of 2 to 3 per second on the right side, which was the side contralateral to the chorea, in the first two records is evident. In the last record, taken six months later when the patient had clinically recovered, there is no such activity.

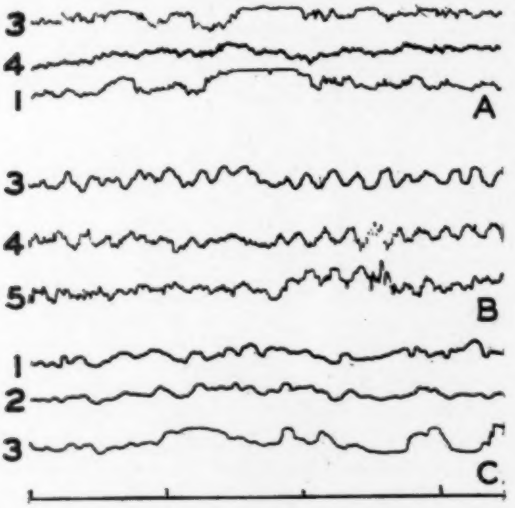

Fig. 8.—Electroencephalograms of patients suffering from chorea. *A*, A case of generalized Sydenham's chorea. Note the irregular activity from both sides of the head; *B* and *C*, Cases of congenital chorea. The 6 per second activity in *B* resembles the cortical pattern in idiopathic epilepsy.

In *C* the activity is more irregular.

The leads are as follows: *1*, Right parietal to vertex; *2*, right occipital to vertex; *3*, left occipital to vertex; *4*, left parietal to vertex; *5*, left frontal to vertex.

The time in seconds is indicated at the bottom of the electroencephalograms.

matic chorea that there was a decrease or absence of the normal alpha rhythms and that there was continuous slow wave activity of increased amplitude. In addition, they found that the more severe the clinical signs of chorea, the more pronounced were the changes in the cerebral activity.

Gibbs and Gibbs[22] present the electroencephalographic findings of several cases of chorea in their atlas. In one case, which they describe as Sydenham's chorea with cortical involvement, 2 to 3 per second waves of great amplitude are seen in records made from leads from all parts of the scalp. As the clinical state of the patient improved, the electroencephalogram became more nearly normal. In other cases they found no abnormality in the records.

THE PATHOGENESIS OF CHOREA

Many explanations have been suggested for choreic movements. The majority are physiologic interpretations of pathologic findings in selected cases of chorea. Charcot's postulation[11] of a special bundle in the internal capsule, which, when damaged, gave rise to choreic phenomena, has received no confirmation in subsequent studies. Monakow[40] found pathologic lesions in the thalamic nuclei and concluded that irritation of the thalamo-cortical fibers caused chorea. Bonhoeffer[6] noted lesions in the superior cerebellar peduncle and emphasized the importance of damage to the cerebello-cortical pathways in the production of choreic movements. Halban and Infeld,[26] studying a case with an isolated lesion of the red nucleus, came to the same conclusion.

Many cases of chorea have revealed at autopsy gross lesions of the basal ganglia. In fact, such lesions have been so well circumscribed (Fragnito and Scarpini,[18] Austregeslio and Borges-Forte,[2] Grünthal and Hartmann,[25] and Davison and Goodhart[12]) that it has been possible by correlating the predominant clinical involvement with the site of the pathologic lesion to deduce a somatotopic localization within the striatum. Such discrete involvement is rarely seen in the choreas of childhood and occurs in the arteriosclerotic or senile choreas. It is thus apparent that the pathologic substrate of chorea is to be found in many different parts of the central nervous system.

Wilson[64] recognized that the lesion in chorea had no single or invariable anatomic site and believed the phenomena to be the result of a disorder of a system. He believed that the cerebello-rubro-thalamo-cerebral pathway and pyramidal tracts played an important role in the production of the hyperkinetic signs. The precise physiologic mechanism governing these involuntary movements Wilson did not suggest, although he concluded that the phenomena originated at the level of the cerebral cortex.

We are inclined to believe that the cerebral cortex plays a fundamental role in the production of choreic movements. In favor of this

thesis is the abnormal activity of the electroencephalogram which we believe is of cortical origin. At times, this abnormal activity is localized to one part of the cerebral cortex, and it is of interest to note that the localization of this activity is in the central region contralateral to the maximum motor disturbances. Were this activity the result of subcortical discharges, one might expect the electroencephalogram to be the same in all leads, but this is not the case. The different leads may show abnormal activity which is neither synchronous nor in a phasic relationship to that of any other lead. This is strong evidence in favor of the assumption that the activity is cortical in origin. Of the entire cerebral cortex it seems most probable that the motor area is the region directly responsible for the production of the choreic movements. It is the only part of the cerebral cortex, in fact of the entire brain, from which, upon electrical excitation, motor phenomena resembling choreiform movements can be elicited.

But the neuropathologist protests that, as we have just shown, the changes in the brains of choreic patients are not confined to the cerebral cortex. They may be minimal there and gross in other parts of the nervous system. The other portions frequently affected are the cerebellum, its efferent pathways, the striatum, and the thalamus. What is the relationship of lesions in these structures to the abnormal functioning of the motor cortex? With recent anatomic and physiologic studies of the motor cortex in primates, this question perhaps can be answered. There is now evidence of at least two circuits impinging upon the motor cortex and playing an important role in its normal function. They are the cortico-ponto-cerebello-dentato-rubro-thalamo-cortical and cortico-strio-thalamo-cortical circuits.

The importance of the first circuit, long recognized, has been recently stressed by Fulton and his school.[19, 20] Both the anatomic and the physiologic aspects of the dentato-thalamo-cortical arm of this arc have been extensively studied. Rossi[48] showed that the threshold of excitation of the motor cortex was lowered when the cerebellum was simultaneously stimulated. As a corollary, Walker[60] demonstrated that electrical stimulation of the cerebellum increased the cortical activity of the motor area on the opposite side.

The second and more recently described circuit that influences the motor cortex, the cortico-strio-thalamo-cortical arc, has been studied by Dusser de Barenne and McCulloch,[15] and Mettler and his co-workers.[38] Mettler has demonstrated that stimulation of the caudate nucleus causes a decrease of the electrical excitability of the cerebral cortex. Dusser de Barenne and McCulloch[15] have shown that excitation of the caudate nucleus inhibits the electrical activity of the motor cortex and conversely that lesions of this nucleus at least temporarily augment the electrocorticogram of the motor area.

It should be realized that there is a constant stream of impulses passing through both of these nervous circuits, even when the organism

appears to be at rest. Volitional innervation is superimposed upon this activity. It therefore seems probable that these circuits maintain the motor cortex in a tonic state so that volitional activity may be easily initiated. It is not necessary, however, that all the neurones of the cerebral cortex, the basal ganglia, or the cerebellum be constantly kept active by this mechanism. Probably only a very small proportion of the neurones are active at any one time, and the majority of the remainder come into play only when the motor cortex is stimulated to activity.

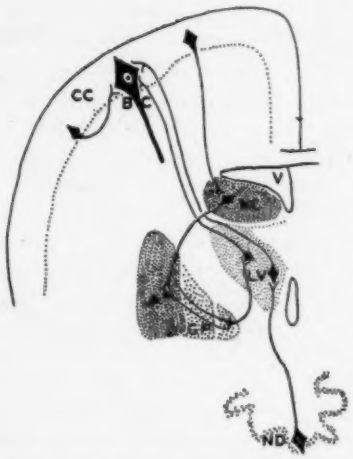

Fig. 9.—Schema of the nervous circuits which modify the activity of the cerebral cortex. Only the efferent limb of the cortico-ponto-cerebello-thalamo-cortical circuit is shown.

BC, Betz cell; *CC*, cerebral cortex; *GP*, globus pallidus; *LV*, nucleus lateralis ventralis; *NC*, nucleus caudatus; *ND*, nucleus dentatus cerebelli; *P*, putamen; *V*, corpus ventriculi.

It is then evident that at least two subcortical circuits may modulate the activity of the motor cortex. In addition, the cortex of the postcentral gyrus and of other parts of the cerebrum influences the activity of the motor area. It is thus apparent that by modifying the influence of any of these mechanisms the motor cortex may be made abnormally sensitive and responsive to what would ordinarily be subliminal stimuli. The presence of lesions in the cerebellum and its efferent pathway, the thalamus, and striatum must interfere with these modulating circuits and conceivably could make the motor cortex abnormally sensitive. It does not seem probable, however, that such lesions furnish the stimulus setting off the abnormally sensitive cortex. In addition to these gross organic changes, diffuse degenerative alterations of the cortical neurones are present in almost every case of chorea. These mild changes are generally conceded to be reversible cellular phenomena. If they were responsible for the stimulation of the motor cortex, the rapid recovery

of the patient could be easily understood. It is postulated that these slightly altered cortical cells may discharge spontaneously and effect a motor response if the cerebral cortex is abnormally excitable. Such responses due to focal irritation of the motor cortex would be of the nature of twitches or jerks, and might occur when a limb is either at rest or in motion. When the cortical neurones recover from these mild degenerative changes which are generally conceded to be reversible cellular phenomena, the choreiform movements would disappear even though the cortex remained hyperexcitable, but they might recur if the cells again were subjected to toxic or infective influences. Recurrent attacks of chorea and the common occurrence of a previous history of a childhood chorea with the chorea of pregnancy are thus readily explained.

There must be another factor influencing the production of the motor phenomena of chorea. Otherwise choreic manifestations should be present at some time in all patients whose brains present the above-mentioned anatomic substrata. However, Bruetsch[9] reported a series of four rheumatic cases from a mental hospital in which the identical brain changes described in Case 2 of this paper were found at post mortem. No history of chorea was present in any case. And Winkelman and Eckel[65] found similar changes in the brains of five patients who died of acute rheumatic fever. Only two of these patients had chorea at any time. Only about 5 per cent of patients suffering from rheumatic heart disease have a history of chorea, but a much larger percentage, if the above studies can be used as a criterion, have "rheumatic brain disease." Why do all of those patients not develop chorea? The answer seems to be that because of individual differences the cerebral cortex never becomes sufficiently excitable to allow the spontaneous discharges of the degenerating neurones to be effective stimuli.

That such individual differences in the excitability of the cerebral cortex do exist appears to be demonstrable if we may use the convulsive state as an analogy. Since convulsions and chorea are not unrelated, such an analogy seems justifiable. It has been found that certain dysrhythmic electroencephalographic patterns are characteristic of the convulsive state, although not all individuals having epileptic attacks show such cortical activity (Lennox[31]). But many of the parents and siblings of epileptics (in fact 10 per cent of the general population) have similar patterns, although they have never had an epileptic attack. It has been suggested that the individuals with cerebral dysrhythmias are potential epileptics and that if they developed an exciting factor, such as a brain tumor or head injury, convulsive seizures might occur. It seems that inactive choreics (Table I) and some of their relatives have similar abnormal electroencephalographic activity (Usher and Jasper[59]) which probably indicates a hyperexcitability of the cerebral cortex. In such cases the anatomic substrata readily lower the threshold by the physiologic mechanisms previously mentioned, to a level at which the spon-

TABLE I

THE ELECTROENCEPHALOGRAPHIC FINDINGS IN CHOREA

INITIALS	AGE (YR.)	TYPE OF CHOREA	ACTIVE OR TIME INACTIVE	ELECTROENCEPHALOGRAM
S. K	14	Sydenham's	Active	Increased irregular activity in all leads
J. R. D.	14	Sydenham's	Active	Increased irregular activity in all leads
P. P.	9	Sydenham's	Active	Increased activity in all leads
E. T.	14	Sydenham's	Active; second attack	Fragmentation of the alpha rhythm with occasional 4 per second waves
C. P.	10	Sydenham's	Active	Increased irregular activity with 4 to 6 per second waves in all leads
H. S.	12	Sydenham's (Hemichorea)	Active	Increased irregular activity in all leads
L. S.	13	Sydenham's	Active	Increased irregular activity in all leads; 1 to 6 per second waves
S. B.	11	Sydenham's	Active	Increased irregular activity; humps and spikes; 1 to 6 per second waves
L. B.	14	Sydenham's	Active	Increased irregular activity; 3 to 5 per second in all leads
C. K.	10	Sydenham's	Active	Increased irregular activity with 3 per second waves in all leads
C. B.	16	Sydenham's	Active	Increased irregular activity with 3 per second waves in all leads
R. H.	13	Sydenham's (Left hemichorea)	Active	One to 3 per second waves in right parietal lead
		Sydenham's (Left hemichorea)	Inactive six months	Normal
D. K.	16	Sydenham's	Inactive one year	Mild irregular activity in all leads
I. C.	11	Sydenham's	Inactive one year	Increased irregular activity with 3 and 5 per second waves in all leads
P. B.	14	Sydenham's	Inactive one year	Mild increased activity in all leads
B. S.	8	Sydenham's	Inactive two years	Moderate increased activity in all leads
F. A.	6	Sydenham's	Inactive two years	Increased irregular activity in all leads
L. D.	13	Sydenham's	Inactive five years	Normal
D. L.	17	Sydenham's	Inactive seven years	Normal
R. P.	7	Sydenham's with major convulsions	Inactive five months	Increased irregular activity with 2 to 6 per second waves in all leads
R. S.	14	Congenital	Active	Increased activity with 2 to 6 per second waves in all leads
T. T.	9	Congenital	Active	Slight irregularities in all leads
E. M.	9	Congenital	Active	Increased activity in all leads with 3 to 6 per second waves
P. P.	9	Congenital	Active	Increased irregular activity with waves 1 to 30 per second, fairly well organized

taneous discharges of the degenerating neurones are effective stimuli. The role played by the congenital and acquired factors probably varies greatly from case to case, the one being almost solely responsible at times and again having little or no part in the production of the phenomena.

We therefore suggest that the cerebral cortex is the level at which the movements of chorea originate, but we believe that these abnormal movements occur only when the motor cortex is hyperexcitable, congenitally or because of lesions in physiologic arcs or circuits, which normally modulate the activity of the cerebral cortex.

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SODIUM SULFATHIAZOLE CLEARANCE AS A MEASURE OF RENAL FUNCTION IN CHILDREN

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ONE of the characteristics of the sulfonamide compounds when introduced into the living body is their rapid elimination in the urine. In chemotherapeutic practice, therefore, maintaining the sulfonamides at an effective level is dependent upon the rate at which the drugs are lost by way of the kidneys as well as through the bowels. In the presence of either too high or too low a concentration of the sulfonamide in the blood, the most important limiting factor is probably the renal excretion of the drug rather than the extent or dosage of medication. These considerations naturally suggest, as the initial step in sulfonamide therapy, the importance of determining the renal function of the patient with special reference to the excretion of the drug. For this purpose a standardized test procedure has been devised to provide a simple means of guiding both the dosage and frequency of sulfonamide medication whereby the minimal toxic dose may be calculated to produce the maximal therapeutic effect. The present report embodies the results of a series of such tests as performed on hospitalized children, and a comparison of these results with those derived from urea clearance tests performed on the same patients demonstrates, within a reasonable range of errors, a relative accuracy of the sulfathiazole clearance as a reliable test of renal function. It must be emphasized at the outset that the sodium sulfathiazole clearance test here described is by no means a substitute for the urea clearance test; it is employed merely as a means of estimating the rate of excretion of the sulfonamide as a guide to therapeutic management of patients.

In principle and application, the use of a sulfonamide for measuring the excretory efficiency of the renal tissue is quite similar to that of phenolsulfonephthalein (phenol red). The amount of intravenously injected sulfonamide eliminated in the urine at stated intervals measures the ability of the kidneys in removing a foreign substance. While excretion of a sulfonamide from the blood stream into the urine depends on numerous factors other than the intactness of the kidney tissue, renal function as a whole may be estimated on the basis of the concentration of the drug in the urine. Marshall[1] stated that the excretion of phenolsulfonephthalein involves primarily the reserve function of the tubular epithelium, while Stieglitz and Knight[2] believe that sodium ferrocyanide is filtered apparently through the glomeruli only. In the case of sulfonamides, Marshall[3] expresses the opinion that, judging from the data available on the clearance of sulfathiazole in both

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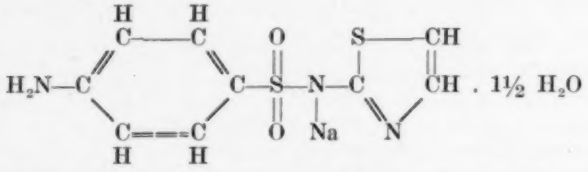
dog and man, the drug is excreted by the kidney entirely by glomerular filtration and that about two-thirds of it is reabsorbed from the glomerular filtrate by the tubules. Furthermore, excretion of sulfonamides is largely influenced by the extent to which they are conjugated in the body, rather than by the degree of renal efficiency, since conjugated drugs are apt to be lodged in the lumen of the uriniferous tubules. It is now well known that the various sulfonamides differ decidedly in the readiness with which they undergo acetylation; hence a test designed to estimate the excretory function of the kidney by use of a sulfonamide should utilize the one least likely to form conjugated compounds to any great degree.

TEST PROCEDURE

The sulfonamide found to be most ideal for the purpose of this test is sodium 2-sulfanilyl-aminothiazole sesquihydrate (Squibb), having the following structural formula:



This compound, being a pure crystalline preparation, is readily soluble in water at room temperature and is not so easily acetylated in the body as to form casts in the kidney tubules. The standard test dose for children between the ages of 5 and 14 years, with body weight varying from about 20 to 50 kg., has been arbitrarily set at 0.1 Gm.; for large or obese children weighing over 50 kg., as well as for adults, the test dose should be doubled in order to obtain satisfactory measurements of the drug excreted in the urine. The test dose may be weighed out on an analytical balance on a clean paper and, just before use, transferred to the barrel of a syringe and mixed with 10 c.c. of sterile distilled water and dissolved by gentle shaking.

In the present series of studies the sulfathiazole excretion test was preceded in each case by a urea clearance test. The patient was given a light breakfast, consisting of fruit, cereal with milk, and a glass of milk (200 c.c.), and some water (100-200 c.c.). One hour after the breakfast the patient's bladder was emptied, the specimen being discarded, and another glass of water (200 c.c.) was given. Collection of the test sample of urine was made exactly sixty minutes later, the patient as a rule remaining quietly in bed during the entire test period. A capillary blood sample for the determination of blood urea was obtained during this sixty-minute period. If the test sample of urine was found to be less than 60 c.c. in amount, it was discarded and an additional amount of water (200 c.c.) was given; a second urine sample was then taken one hour later, which in most instances amounted to

over 100 c.c. The quantitative determination of urea concentration in both blood and urine was made by the micromethod herein described.

Upon obtaining a satisfactory sample of urine for urea estimation, at once 0.1 Gm. of sodium sulfathiazole dissolved in 10 c.c. of sterile distilled water was injected slowly into the antecubital vein. Following this injection of the test drug, two urine samples were collected at hourly intervals (Specimens I and II), one glass of water being given after the first collection to insure an adequate urinary flow. A quantitative estimation of the sulfonamide in each of the two specimens of urine was made by the microadaptation of the original Bratton-Marshall method,[4] using the new coupling reagent. The most accurate results were obtained from urinary samples measuring from 4 to 6 ounces (120-180 c.c.), for when the amount of urine falls below this level, the drug is so greatly concentrated as to make proper dilution difficult and thus subject to the introduction of possible technical errors.

CHEMICAL METHODS

1. Microsulfathiazole Method.—For the performance of the microsulfathiazole technique, the following reagents are required:

1. Normal solution of hydrochloric acid.
2. Sodium nitrite, 0.1 per cent aqueous solution, prepared fresh each week.
3. Sodium sulfamate, 0.5 per cent solution in water.
4. N-(1-naphthyl)-ethylene-diamine dihydrochloride (Eastman Kodak Co.), 0.1 per cent aqueous solution.
5. Trichloroacetic acid, 15 per cent aqueous solution.

For the determination of urine sulfathiazole, 0.1 c.c. of the sample is mixed with 4 c.c. of distilled water in a clean test tube and acidified with 1 c.c. of normal hydrochloric acid solution. Diazotization is accomplished by the addition of 0.5 c.c. of 0.1 per cent sodium nitrite solution; three minutes afterward excess nitrous acid is destroyed by adding 0.5 c.c. of 0.5 per cent sodium sulfamate solution, two minutes being allowed for this reaction. Within a few seconds after adding 0.5 c.c. of the coupling reagent, a permanent rose color develops which can be read after about five minutes. The concentration of the sulfonamide is then calculated from a standard curve calibrated from known concentrations of the pure compound which had been treated in the identical manner as the unknown.

Blood sulfonamide is determined by exactly the same procedure as above described, except that the blood protein is first removed by precipitation with 1 c.c. of 15 per cent trichloroacetic acid after 0.1 c.c. of capillary blood has been hemolyzed in 4 c.c. of distilled water.

The above procedure measures the amount of free sodium sulfathiazole in both blood and urine. In order to determine the amount of combined sulfonamide, the diluted urine or blood filtrate is acidified with 1 c.c. of normal hydrochloric acid solution and then digested for one hour at 100° C., either in the oven or over a water bath. During this process the test tubes must be stoppered, and the original volume in each tube must be restored with distilled water after digestion. The difference between the total and free sulfonamides is the amount of combined form in either sample.

2. Microurea Method.—For calculation of the urea clearance values, the original method of Möller, McIntosh, and van Slyke[5] was employed, the urinary velocity having been corrected by means of the chart published by McIntosh, Möller, and van Slyke[6] and based on the height of each individual studied. The chemical

method here used is based on direct nesslerization of ammonia nitrogen derived from urea by the action of urease. The reagents required for this micromethod are:

1. Sodium citrate, 0.3 per cent aqueous solution.
2. Sodium tungstate, 10 per cent aqueous solution.
3. Sulphuric acid, $\frac{2}{3}$ N solution.
4. Phosphate buffer solution (5.6 Gm. sodium pyrophosphate and 0.8 Gm. metaphosphoric acid in 100 c.c. distilled water).
5. Nessler-Folin reagent (Koch modification[7]).
6. Glycerol urease, prepared from jack bean meal (Koch[7]).
7. Permutit.

Blood urea determination was made by first hemolyzing 0.1 c.c. of capillary blood in 5 c.c. of a 0.3 per cent solution of sodium citrate in a 15 c.c. centrifuge tube and converting urea into ammonia by the addition to the hemolyzed sample of one drop each of phosphate buffer and of undiluted glycerol urease, allowing at least ten minutes for the complete reaction to take place. Deproteinization was then accomplished by adding 0.5 c.c. each of 10 per cent sodium tungstate and $\frac{2}{3}$ N sulfuric acid solutions. After the proteins were completely precipitated, the mixture was centrifuged for about five minutes at approximately 2,000 revolutions per minute, the clear supernatant fluid then transferred quantitatively into another clean test tube and 0.6 c.c. of Nessler-Folin reagent added. The yellow color immediately developing in the sample was read at once in the Leitz-Maas photoelectric colorimeter and the urea nitrogen calculated from the standard curve previously prepared from a series of pure ammonium sulfate solutions.

For determining urine urea, 1 c.c. of the sample, diluted with 9 c.c. of distilled water, was first treated with 1 Gm. of permutit in order to remove preformed ammonia; the diluted specimen was then filtered, and 0.1 c.c. of it was mixed with 5.3 c.c. of distilled water in a clean test tube. Ten minutes were allowed for the conversion of urea into ammonia after the addition of one drop each of phosphate buffer and undiluted glycerol urease. The orange-yellow color developing upon the addition of 0.6 c.c. of Nessler-Folin reagent was immediately read in the same colorimeter and the urea concentration calculated from the same standard curve used in determining the blood urea concentration.

RESULTS AND COMMENT

The sodium sulfathiazole clearance test, as described in the foregoing paragraphs, was performed on a total of forty-six children, including seven patients with either suspected or known renal pathology. The results of these tests are presented in Tables I and II, in which comparisons are made with the determinations of urea clearances on the same individuals just prior to the intravenous injection of the test drug. No particular criterion was used in the selection of test cases, these children being in the hospital for treatment or observation with relatively mild or chronic diseases. No acutely ill patients were studied nor were any under sulfonamide therapy included in this series. In a few instances, the children had previously received specific chemotherapy, but in these cases the urine was first tested to make certain of its complete freedom from any remaining trace of the drug.

In conjunction with the performance of these tests, a series of preliminary observations was made on another group of hospitalized patients with reference to the elimination of sodium sulfathiazole after

TABLE I

EXCRETION OF SODIUM SULFATHIAZOLE DURING TWO HOURS IN THIRTY-NINE HOSPITALIZED CHILDREN WITHOUT KIDNEY PATHOLOGY COMPARED WITH UREA CLEARANCE TESTS

DIAGNOSIS	SEX	AGE (YR.)	SODIUM SULFATHIAZOLE EXCRETED IN TWO HOURS (MG. OR %)	UREA CLEARANCE (% NORMAL)
Neurodermatitis	M	14	37.1	110
Diarrhea	F	12	34.8	102
Hyperkeratosis	F	10	34.5	86
Section of facial nerve	F	11	32.1	70
Abdominal edema	M	12	31.7	140
Deficiency, vitamin	M	10	31.5	140
Bronchial asthma	F	11	28.0	104
Hyperthyroidism	F	13	27.2	124
Rheumatic heart disease	M	9	26.9	79
Bronchial asthma	M	9	26.4	112
Epidermophytosis	F	11	26.2	86
Observation	M	8	25.7	115
Rheumatic heart disease	M	14	25.4	105
Obesity	M	12	24.6	60
Bronchial asthma	M	13	24.5	55
Encephalography	M	14	24.4	89
Dwarfism	F	5	24.4	80
Behavior problem	F	8	24.3	80
Acne vulgaris	M	14	24.2	100
Chronic leucemia	M	12	24.0	80
Tuberculous contact	F	12	23.8	91
Chronic rickets (?)	F	9	23.2	92
Cervical adenitis	M	6½	22.4	91
Rheumatic heart disease	M	9	22.1	79
Chronic diarrhea	M	10	21.4	127
Mental retardation	M	14	21.2	122
Bronchial asthma	M	14	20.8	115
Visceral xanthomatosis	F	14	20.8	74
Spina bifida	M	12	20.5	115
Plastic surgery	F	14	20.4	96
Lymphosarcomatosis	M	12	20.0	84
Streptococcus infection	F	5	19.7	80
Mastoiditis	F	11	19.4	64
Obesity	M	10	19.4	81
Rheumatic heart disease	F	10	18.7	79
Bronchial asthma	F	11	18.5	98
Mitral stenosis	F	14	16.9	99
Rheumatic heart disease	M	11	15.0	62
Diarrhea	F	14	14.5	70

TABLE II

EXCRETION OF SODIUM SULFATHIAZOLE DURING TWO HOURS IN SEVEN HOSPITALIZED CHILDREN WITH RENAL PATHOLOGY COMPARED WITH UREA CLEARANCE TESTS

DIAGNOSIS	SEX	AGE (YR.)	SODIUM SULFATHIAZOLE EXCRETED IN TWO HOURS (MG. OR %)	UREA CLEARANCE (% NORMAL)
Acute hemorrhagic nephritis	M	9	20.1	46
Nephritis (?)	F	14	18.9	67
Floating kidneys (?)	F	9	18.8	69
Chronic nephritis	F	10	17.8	48
Chronic nephritis	M	14	17.2	35
Acute nephritis	F	6	13.5	60
Nephrosis	M	4	7.5	51

oral and intravenous administration. Representative data showing the minimal and maximal excretion of the drug during the twenty-four hours following the administration are given in Table III. It is apparent that, while there is considerable variations in this regard from patient to patient, in the urine of children with a normal renal function, up to 75 per cent of the injected drug may be expected to be recoverable; in those with definite renal pathology the elimination may be reduced fully 50 per cent of the expected amount. The lowest excretion encountered was in one instance of acute hemorrhagic nephritis, in which the amount recovered in the twenty-four-hour urine specimens was only 33.17 per cent of the injected drug. Another case of abnormally low excretion (37.51 per cent) was that of a male child 11 years old suffering from acute rheumatic heart disease. Although the relationship existing between the cardiac pathology and renal function

TABLE III

TOTAL TWENTY-FOUR-HOUR EXCRETION OF SODIUM SULFATHIAZOLE IN FOUR REPRESENTATIVE CASES, SHOWING MINIMAL AND MAXIMAL VALUES (TEST DOSE, 0.1 GM.)

HOURS AFTER INJECTION	MINIMAL EXCRETION (MG. OR %)		MAXIMAL EXCRETION (MG. OR %)	
	CASE 1	CASE 2	CASE 3	CASE 4
1	11.24	10.25	21.50	14.50
2	2.20	7.20	10.40	9.20
3	5.70	4.32	6.00	5.76
4	3.50	4.08	5.46	4.18
6	3.92	No specimen	No specimen	7.70
9	1.08	4.83	15.75	3.84
14	3.57	3.90	2.80	4.83
18	0.90	1.68	3.38	2.16
24	1.05	1.25	1.44	0.80
Total	33.17	37.51	66.23	73.23

Case 1. Female, 5½ years old; diagnosis, acute hemorrhagic nephritis.
Case 2. Male, 11 years old; diagnosis, acute rheumatic heart disease.
Case 3. Female, 12 years old; diagnosis, rheumatic heart disease with pleural exudate.
Case 4. Male, 12 years old; diagnosis, malnutrition.

in this patient is merely speculative, it is reasonable to assume that during the acute stage of heart disease a significant reduction in the excretory ability of the kidney may occur, based probably, in part at least, on the disturbed hemodynamics. On the other hand, in the maximal excretion group was found a female child also with rheumatic heart disease, complicated by pleural effusion, who showed no evidence whatever of impaired renal function, as judged by the sulfathiazole clearance test. Unfortunately, urea clearance tests in both these children were not performed. Generally speaking, the average normal excretion of sulfonamide through the urinary tract during the twenty-four-hour period following administration may be safely regarded as ranging from 55 to 60 per cent. When the excretion is reduced to one-half of this normal range, either temporary or permanent renal pathology may be suspected.

Sodium sulfathiazole introduced into the blood stream is rapidly eliminated from the body and the greatest and most significant excretion occurs during the first two hours following the administration. This period, then, may be conveniently taken as the test period, the average normal value being from 20 to 30 per cent of the injected drug. In cases of renal diseases, the excretion is usually below the minimal normal level of 20 per cent, although it must be remembered that even in individuals with no suspected renal pathology the excretion of the drug during the test period may be abnormally low. An individual showing a significant reduction in sulfonamide clearance requires further studies with special reference to the possibility of either early or impending kidney disease.

The question as to whether or not sodium sulfathiazole undergoes excessive acetylation in the body, thereby influencing the renal threshold, cannot be answered with complete assurance. Marshall[3] has stated that sulfathiazole is probably acetylated to a less extent in man than either sulfanilamide or sulfapyridine. The only way by which this question can be answered would be to make separate analyses of blood and urine for both free and combined forms of the sulfonamide, but even then a complete answer cannot be found in such data. Nevertheless, a few illustrative results of such analyses are given in Table IV, from which it is clear that in this particular patient, with an apparently normal renal function, a little over 17 per cent of the excreted sulfonamide was in the combined form.

TABLE IV

EXCRETION OF TOTAL, COMBINED, AND FREE SODIUM SULFATHIAZOLE AFTER INTRAVENOUS INJECTION OF 0.1 GM.

HOURS AFTER INJECTION	SODIUM SULFATHIAZOLE EXCRETED IN URINE (MG. OR %)		
	FREE	COMBINED	TOTAL
1	15.60	1.43	17.03
2	12.00	2.40	14.40
3	5.98	1.84	7.82
4	4.06	2.10	6.16
Total	37.64	7.77	45.41
Per cent	82.9	17.1	100

Comparison of results obtained by the sulfathiazole and by the urea clearance tests reveals a fair degree of correlation; absolute agreement is not to be expected, since these tests measure separate and distinct functions of the excretory mechanism. In both these tests the velocity of urinary flow is the chief factor which influences the final results; hence during the conduct of the test it is essential that free diuresis be maintained by administering a glassful of water after each sample is collected. The most accurate results have been obtained when the hourly specimens are sufficient to yield a velocity of at least 2 c.c. per minute. If the samples are too voluminous, the results are likely to be

too low, while highly concentrated specimens give too high values. Such manipulations as diluting or concentrating the original specimens are apt to augment technical errors.

Finally, the specific purpose for which the sodium sulfathiazole test has been devised must be emphasized. As already referred to, this test is not a substitute for any of the standard approved tests of renal function. Although the test is similar both in principle and application to the well-known phenolsulfonephthalein test, the sulfathiazole clearance test is particularly useful in patients who are to be treated with any of the sulfonamide drugs. This test may be performed as a preliminary procedure in the therapeutic scheme, especially in patients with either known or suspected renal pathology, and it may be repeated at frequent intervals during the course of the treatment. The only necessary condition for the performance of the test is the temporary withdrawal of the therapeutic medication. Complete removal of the drug from the body, in the presence of adequate diuresis, is usually effected within twenty-four to thirty-six hours after cessation of the administration. By performing the test whenever indicated, the chemotherapy may be rationally guided and controlled.

SUMMARY AND CONCLUSIONS

A simple and satisfactory test for measuring the excretory function of the renal tissue is described. This method simply estimates the rate at which the intravenously injected sulfonamide is eliminated from the blood stream by way of the urinary tract during a stated period of observation. Following the intravenous administration of 0.1 Gm. of sodium sulfathiazole dissolved in 10 c.c. of sterile distilled water, normal children between the ages of 5 and 14 years excrete from 20 to 30 per cent of the injected substance during the first two hours. In patients with definite renal pathology, the amount of substance excreted during the same period may fall far below the minimal normal level, although variations from this rule are encountered in both normal and pathologic cases. When compared with the results of urea clearance tests conducted on the same children just preceding the sulfathiazole tests, there seems to exist a reasonable degree of correlation between the two.

The sodium sulfathiazole clearance test is especially useful in cases of renal diseases in which complicating infections frequently call for the specific chemotherapy, as well as in those of bacterial infections in general for which the sulfonamides are indicated for treatment. In all these cases the sodium sulfathiazole clearance may advantageously be determined as the initial step in the scheme of therapy, and the test may be repeated at frequent intervals for estimating the extent of renal complications whenever any signs or suspicions of their presence arise. It should be remembered in this connection that the urea nitro-

gen cannot be estimated by the nesslerization technique in patients under sulfonamide therapy, since the drug itself gives the same yellow color with the Nessler-Folin reagent. Under these circumstances some other suitable chemical methods for urea determination must be employed. Likewise, the sulfathiazole clearance test cannot be performed unless the body fluids are first made free of traces of the drug.

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OXYCEPHALY

Results of Treatment by the King "Morcellation" Method

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IN 1938, King reviewed the various operative procedures previously advocated for the relief of increased intracranial pressure secondary to oxycephaly[1] and described an original procedure more fitted to the symmetrical expansion and further growth of the brain and skull. The operation consisted, as performed in the initial instance, of the two-stage formation of a mosaic of the bones of the vault of the skull, a procedure which might be termed "morcellation of the skull."

Recently[2] King has reported the later course of the first patient, operated upon Nov. 10, 1936, a second case of his own, and two cases (Cases 3 and 4) of mine. In this present paper a fifth case of oxycephaly treated by morcellation of the skull will be described, and the results of the treatment of oxycephaly by this simple method will be discussed.

J. S., 11 years of age, colored, was admitted to the Pediatric Service of the Duke Hospital on May 21, 1941, with complaints of headache, progressive loss of vision, bilateral exophthalmus, and deformity of the skull, a group of symptoms and signs observed by the parents over a period of three years before admission. His father and mother were living and well. There were two sisters and two brothers living and well. No similar disorder was reported in other members of the family. This child was born on March 18, 1930, at term, following a labor of four hours. Instrumental delivery was carried out with the use of low forceps, and the child was reported to be normal in all respects at birth. There was no cyanosis and no postnatal convulsions occurred. Development was reported as being normal and the child started school at the age of 7 years and at the time of admission was in the fourth grade. He continued at school until four months before admission when he was forced to withdraw because of headache. The patient had chicken pox and whooping cough at the age of 8 years, measles at 7, and mumps at 6.

Three years before admission the patient began to complain of generalized headache associated with vomiting, the first episode of which followed an attack of whooping cough which lasted for about five weeks. The headache occurred upon arising from bed in the morning and lasted for about one or two hours and then gradually disappeared. Until three years ago the child, as far as the parents had observed, was quite normal in all respects. They had noticed no structural abnormalities of the skull and no changes in the eyes. Following the development of headache, the parents noticed a slow but progressive enlargement and prominence of both eyeballs, and at this time the patient began to complain of gradual diminution in vision, more marked in the left eye. One year following the onset of headache and diminution in visual acuity, the parents became aware of a moderate deformity of the skull and stated that the boy's head did not seem to be enlarging as rapidly as the heads of their other children. They also noticed that it was somewhat flat laterally and more narrow on top than the conformation that they considered to be normal. During the second year of his illness he was quite free of headache and it was not until four or five months prior to admission that the

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headache again recurred and forced him to discontinue school. With recurrence of the headache, the child began vomiting and complained bitterly of generalized throbbing headache. For two months vision had been completely lost in the left eye. During this time he had complained of diminished hearing in the left ear. The parents state that there had been no evidence of mental deterioration and that the child had been just as alert as ever. No other history of neurologic defect could be elicited.

Admission examination showed a well-developed and well-nourished colored boy of 11 years with obvious bilateral exophthalmus and an obvious deformity of the cranial vault. In a general physical examination, shotty and discrete submaxillary nodes were palpable. The mucous membranes of the nose were pale and moist and somewhat edematous. There was a continuous serous discharge from the nose. The tonsils were enlarged and reddened. The teeth were moderately carious. No other gross skeletal abnormalities were noticed. The significant physical findings were, therefore, restricted to those present in the head.

The head was obviously smaller in all diameters than was normal for the child's age. It was somewhat flattened laterally, presenting an inverted V-shaped deformity. There was a narrow bony ridge running the entire length of the sagittal suture from the coronal to the lambdoidal suture. The following skull measurements were made: suboccipitofrontal circumference, 48 cm.; suboccipitobregmatic circumference, 47 cm.; occipitofrontal circumference, 49 cm.; mentovertex circumference, 57 cm.; occipitomento circumference, 58½ cm. There was no localized area of tenderness. No bruit was heard. In the region of the anterior fontanel there was a moderate prominence. The forehead was rather receding and the occiput flat. The superciliary ridges were inconspicous. There was no abnormality of the nose, maxilla, or hard palate. There was a moderate exophthalmus, with the left orbit being more prominent than the right.

Neurologic examination showed an intact sense of smell. Vision in the right eye was 20/80, and vision in the left eye was restricted to light perception. The peripheral visual field in the right eye was moderately constricted. Both optic discs were very pale, with the left disc presenting the picture of a primary optic atrophy. The neuroretinal outlines were quite distinct. The peripheral retinas showed no change from normal and the retinal vessels appeared normal. There was a moderate external deviation of the left eye, and the left pupil reacted sluggishly to light stimulation. The left corneal reflex was diminished and hypalgesia and hypaesthesia were present over the domain of the left fifth nerve. Hearing was diminished in the left ear to air and bone conduction. Audiometer tests were unsatisfactory.

Routine blood and urine studies showed no abnormal variations. The blood Wassermann and Kahn reactions were negative. Anteroposterior and lateral stereoscopic films of the skull showed an extreme degree of convolutional atrophy. All suture lines were closed. The dorsum sella appeared completely eroded. The anterior fossa was quite shallow. Electroencephalography carried out upon the morning of operation was reported as follows:

May 27, 1941. "During the resting state, waves of not enlarged amplitude but of distorted form and with unstable abruptly changing frequencies are present over both parieto-occipital regions, slightly more over the right side than over the left. Over the other regions the pattern is fairly normal although at times periods of slight irregularity may occur. Overventilation immediately produces large 3 per second waves in all leads, first in short bursts, later in long runs. After the end of the procedure the large, slow waves at once disappear, but as regards the form of the pattern it remains more irregular than originally for more than forty seconds."*

*Electroencephalographic readings in this case and others discussed in this paper were made by Dr. Hans Loewenbach of the Department of Psychiatry, Duke Hospital.

Formal psychometric tests were not carried out in this individual. There was no history of abnormal mental development, and the child had been carrying out his school duties in the fourth grade quite adequately until his progress was arrested by diminution in vision. In view of these findings, a clinical diagnosis of delayed oxycephaly was established.

Operation.—First-stage morcellation of skull. King operation right. Under bactericidal radiation. Under avertin and ether anesthesia.

"This child had a very typical oxycephaly with complete blindness in the left eye, partial loss of vision in the right to 20/80, with bilateral exophthalmus, with typical changes in the plain x-ray picture, and with an electroencephalogram suggestive of increased intracranial pressure.

"Under local anesthesia a lumbar puncture was done in the third lumbar interspace. Clear fluid was obtained. The initial subarachnoid pressure varied between 240 mm. and 270 mm. of water. There was a rapid rise and fall upon compression of each internal jugular vein. Five cubic centimeters of fluid were preserved for chemical study.

"After induction of the anesthesia and after the usual preparation, a scalp incision was marked out beginning 4 cm. caudal to the lateral portion of the orbit, running mesially to the midline, caudally to a point 4 cm. rostral to the inion and then sweeping laterally to an area 3 cm. posterior and above the mastoid process. The scalp flap was incised and turned back, leaving the pericranium in place. All bleeding points were controlled with the electric cautery. In the posterior third of the scalp incision we encountered a large venous sinus passing from the region of the longitudinal sinus through the bone and then dividing into two smaller venous channels passing into the scalp. In the right occipital region just above the inion and to the right of it was a large collapsible mass perhaps 2 cm. in diameter and projecting 1 cm. above the scalp which also represented a venous lake. The attachment of the temporal muscle was then divided and the squamous portion of the temporal bone was resected, forming a small decompression. The dura was not opened. The dura was under considerable pressure and a distinct herniation of the brain developed which extended above the outline of the bony defect. The morcellation was then marked out as noted in the sketch, in the kodachrome pictures, and in the motion picture taken during the procedure. An effort was made to form a fairly large flap of bone frontally and a rather large diamond-shaped mass of bone lying over the longitudinal sinus. This, of course, will have to be completed at the second stage. Perforator openings were made at appropriate points, and two bony dissections were made across the longitudinal sinus for a distance of 2 cm. beyond the midline. Instead of using the De Vilbiss rongeur for this, we used in its place a small mastoid rongeur which appeared to be a safer procedure to us. At our last morcellation, the De Vilbiss instrument had torn the longitudinal sinus with resultant brisk hemorrhage. The remainder of the morcellation was carried out with the De Vilbiss, and it was astonishing to see the amount of elevation and separation of the bony fragments due to increased intracranial pressure. The temporal fascia was sutured to the pericranium of the morcellated fragments adjacent to the decompression. The galea was then closed with interrupted fine black silk sutures. There was considerable tension but not as much as there had been in our last case. The skin was then closed with interrupted fine silk sutures and the wound dressed in the usual fashion. At the end of this procedure it was amazing to see the diminution in the extent of the exophthalmus on the right side."

Wound healing was uneventful, and the patient was discharged ten days following operation after the application of a light plaster head cast. At this time electroencephalography was reported as follows:

"Compared to the preoperative records of May 27, 1941, today's pattern is almost within normal limits. The amplitude is small, decidely irregular forms are

absent, and there is an indication of alpha activity over both occipital regions. Overventilation in contrast to the preoperative findings has no influence upon the pattern. This is an essentially normal cerebral electroactivity." (Fig. 1.)

The patient returned to the Duke Hospital on Oct. 20, 1941, for the second-stage procedure.

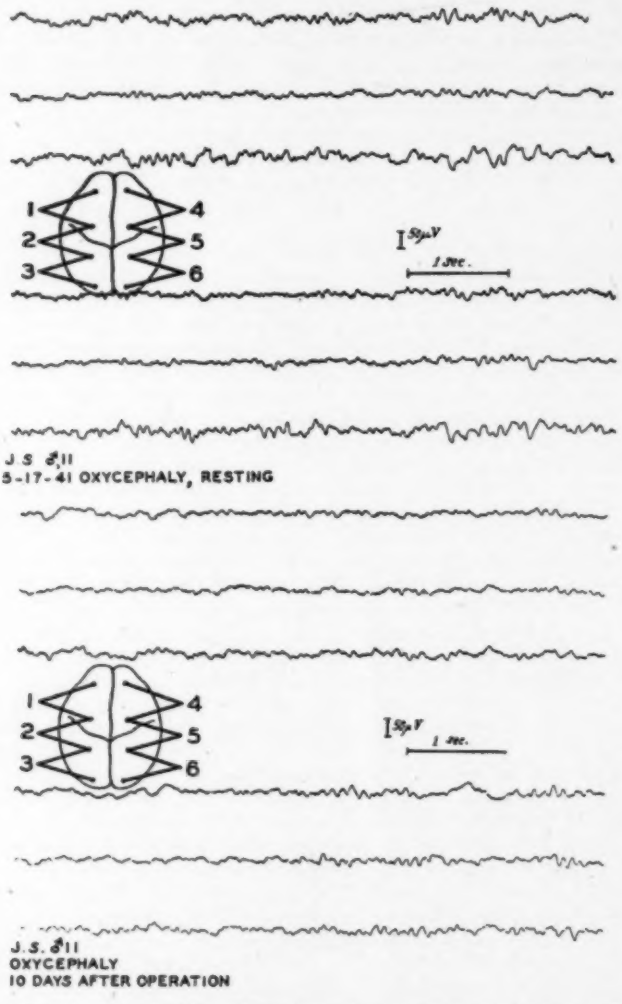


Fig. 1.—Preoperative and postoperative electroencephalograms.

Since discharge he had had no headache, nausea or vomiting, and believed that the vision in his right eye had improved. No improvement had been manifest in the blind eye. Examination of the head showed a definite asymmetry with the right side more rounded than the left. The right frontal boss was also slightly more prominent than the left. Firm pressure over the right side of the skull

showed fairly firm but not complete union of the morcellated fragments. Head measurements were recorded as follows: suboccipitofrontal circumference, 51½ cm.; suboccipitobregmatic circumference, 47 cm.; occipitofrontal circumference, 51 cm.; mentovertex circumference, 63 cm.; occipitomento circumference, 59 cm.; bitemporal vertex, 33 cm.; inion to nasion, 35 cm., an indication of a definite expansion of the skull. The exophthalmometer readings with the instrument set at 100 mm. showed 17 mm. in the right eye and 17 mm. in the left eye. The exophthalmus was still fairly marked. Vision in the right eye was now 20/70, but there was no improvement in the light perception remaining in the left eye. Other findings were unchanged. Stereoscopic lateral roentgenograms of the skull showed the operative procedure and, in comparison with the views taken immediately after operation, showed some increase in the spaces between the bony fragments with, in some areas, evidence of new bone formation. Electroencephalography on the day before operation was reported as follows:

October 23, 1941. "The resting record is irregular but definite pathologic forms are absent. Over the right hemisphere many fast frequency waves appear, probably a sign of greater cortical activity. Alpha waves are completely absent however. Overventilation produces spiky and enlarged waves which are again more pronounced over the right side. Occasionally bursts of spikes occur, lasting two to three seconds. Afterward the pattern returns to its original form in a rather short period. This is irregular and unstable electroactivity; it is asymmetrical, and there are no signs of increased intracranial pressure."

Operation.—Morcellation of skull left. Second-stage King operation for oxycephaly. Under bactericidal radiation. Under avertin and ether anesthesia.

"This boy had had a very nice result from the first stage of his procedure.

"The left side of the skull was prepared in the usual manner. An incision was outlined, duplicating the incision on the right side, and along the midline our incision ran through the former scar. The scalp flap was then reflected. There was the usual increase in vascularization along the midline where healing had produced granulation tissue. The insertion of the temporal muscle on the left side was then divided with the cautery and the muscle reflected from the squamous portion of the temporal bone. A modified subtemporal decompression was then made in this region. The dura protruded rather markedly. Morcellation was then marked out as is our usual custom. At the first procedure the midline had been cut across rostrally and caudally, and our first bony dissection at this time ran from two trephine openings to the midline sections noted above. When these sections were completed, the large area of bone overlying the longitudinal sinus moved easily, indicating that this area will be relieved of underlying pressure. Morcellation was then carried out as usual between other trephine openings. There was rather marked intracranial pressure and the bone fragments separated considerably. The scalp flap was then resutured with interrupted fine black silk sutures and the scalp closed with similar sutures. His condition remained excellent throughout this procedure. A small blood transfusion was given to replace the minimal fluid and blood loss incident to operation."

His postoperative convalescence was quite uneventful, and the boy was discharged after the application of the usual head cast eleven days following operation.

The patient returned two months after operation for removal of the head cast. During this period, he had remained asymptomatic and was eager for permission to re-enter school. His mother stated that the child's behavior was normal and his general condition improved. The skull appeared more symmetrical at this time although the expansion was more perceptible over the right frontal regions in the area which had been morcellated at the first stage procedure. The measurements of the head had not increased above ½ cm. in any diameter, but the skull appeared molded in a more symmetrical form, the left half expanding with some loss of the previously asymmetrical expansion on the right side. The morcellated fragments

were not fused, and the bilateral subtemporal dural openings were commencing to reossify (Fig. 3). Direct vision was measured on several occasions with the readings varying between 20/70 and 20/200 and the difficulty in obtaining accurate records at this age must be recognized. The exophthalmometer readings were unchanged. Electroencephalography on Jan. 7, 1942, was recorded as: "In today's records the form of the waves is, for the most part, rounded, the frequency is far more stable, and the amplitude remains well within the limits of normal. Compared with records taken on May 27, 1941, June 6, 1941, and Oct. 23, 1941, there is in today's records evidence of far greater regularity and stability of the cerebral electroactivity."

DISCUSSION

Oxycephaly may be defined as a congenital malformation of the skull in which premature synostosis of two or more cranial bones occurs, causing increased intracranial pressure. The narrowness and diminution in anteroposterior diameter of the skull are credited to the premature closure of the sagittal and coronal suture lines, and the height of the vault may be due to compensatory expansion of the brain upward through the area of the anterior fontanel, since it cannot expand laterally or in the anteroposterior direction. With the premature obliteration of the cranial suture lines, growth of the brain initiates increased intracranial pressure with the production of headache, papilledema, followed by optic atrophy, exophthalmus from reduction of the depth of the orbit, and convolutional atrophy, as recorded in roentgenograms of the skull.

The mechanism responsible for the development of oxycephaly, and allied congenital malformations of the skull including acrobrachycephaly, scaphocephaly, and perhaps the craniofacial dysostosis of Crouzon, has been discussed in detail in the scholarly paper written by Parks and Powers,[3] which includes comments upon the theories presented earlier by Virchow and Thoma. Since it appears evident that a generalized synostosis of the suture lines is necessary for the production of headache, visual loss, and exophthalmus, surgical interest must be restricted to a study of oxycephaly.

Grieg[4] has distinguished three types of oxycephaly.

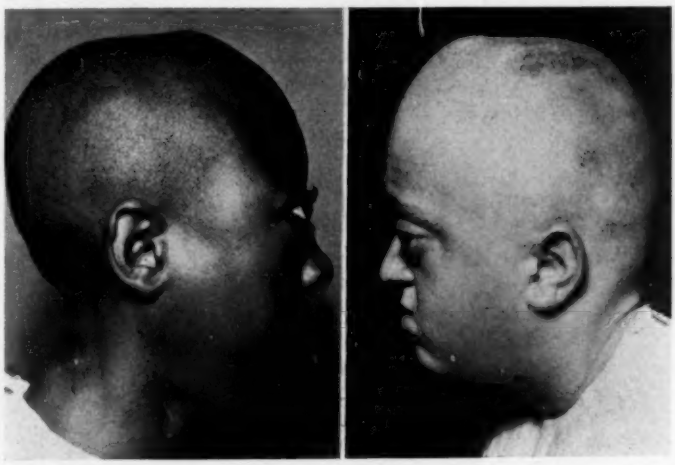
1. True oxycephaly is congenital and is associated with a generalized craniofacial dysostosis and may be accompanied with syndactylism and other deformities of the extremities. Cases 1, 2, and 4 of our series, the last untreated, appear in this category and greatly resemble the craniofacial dysostosis of Crouzon discussed by Ford[5] (Fig. 2). In our patients true oxycephaly was associated with a peculiar beaklike nose, hypoplasia of the maxilla, prognathism, optic atrophy, and exophthalmus.

2. Delayed oxycephaly may appear at any time during the period of brain growth and is never associated with deformities elsewhere in the body. In this category may be placed our Case 3, presented in detail in this paper (Fig. 2), and Case 5, untreated. In the last case, a fairly typical oxycephalic deformity with characteristic x-ray changes is un-

associated with any clinical disturbance with the exception of a mild degree of exophthalmus and diminution of vision to 20/40 in each eye.

3. False oxycephaly, which is a localized synostosis due to incidental disease of the cranial bones, an instance of which has not been recognized in this hospital.

Studies of the clinical course and clinical findings in this series of five cases of true and delayed oxycephaly are summarized in Table I.



A. *B.*

Fig. 2.—*A*, Delayed oxycephaly, present case (Case 3 in Duke series); *B*, true oxycephaly (Case 2 in Duke series).

From a consideration of the clinical findings in these patients, it seems obvious, to repeat the statement made by King, that the ideal operative procedure should be designed to increase the intracranial space in a symmetrical fashion, to preserve the bony covering of the brain, to reduce the exophthalmus, and to preserve vision. These remain the indications for operation, and the results noted in our three patients in whom the operation has been completed form convincing evidence of the efficacy of morcellation of the skull for these purposes.

No contraindication for operation appears to exist. The mental status of patients with oxycephaly in all probability is not unduly influenced by any factor other than that of intracranial pressure, and in our present state of knowledge, operation should not be denied to children with mental retardation. This impression, developed through our personal observations, it confirmed by the statement by Parks and Powers that "The intelligence of the majority of the subjects of the malformation appears to have been normal. In some of them, particularly in those who had found their way into institutions, the intelligence is described as subnormal. Doubtless a number of these latter became institutional inmates as the result of an inability to support

themselves on account of the deformities of the extremities, or had been abandoned in early childhood for reasons of the unprepossessing appearance."

We have not encountered a patient with oxycephaly with complete visual loss, but we should not consider this finding a contraindication to operation if other evidence of increased intracranial pressure were present; i.e., headaches, mental retardation, or convulsions. In Case 5, the visual diminution has been constant for a period of one year, and in the lack of other disturbances, morcellation of the skull has been deferred.

TABLE I

	CASE AND AGE				
	1 M. McK.-5	2 T. C.-13	3 J. S.-11	4 S. T.-1	5 C. B.-8
Type of oxycephaly					
True	×	×		×	
Delayed			×		×
Symptoms					
Headache	×	×	×	?	×0
Visual changes	×	×	×	?	×
Mental dullness	×	×	0	?	0
Convulsions	0	×	0	0	0
Physical findings					
Skull deformity	×	×	×	×	×
Exophthalmus	×	×	×	×	×
Visual changes	20/40 20/40	20/200 20/300	20/80 0	Papill-edema	20/40 With glasses 20/40 With glasses
Prognathism	?	×	0	0	0
Beaklike nose	?	×	0	×	0
Hypoplasia, maxilla	×	×	0	×	0
Deformity of hard palate	×	×	0	×	0
Other deformities	0	0	0	0	0
Initial subarachnoid pressure	0	240	270		
X-ray findings					
Generalized synostosis	×	×	×	×	×
Incomplete synostosis	0	0	0	0	0
Convolutional atrophy	×	×	×	×	×
Encephalography	0	×	0	0	0
Electroencephalography	×	×	×	0	0
Psychometric evaluation	0	Low moron	Not necessary	0	Not necessary
Operation	King	King	King	Previous operation	0

The choice between one-stage or two-stage morcellation of the skull rests with the experience of the individual operator. In older children, such as those in our series, a two-stage procedure has been safe and technically satisfactory. The completed stage is illustrated in this paper (Fig. 3) and fully discussed by King.

A short discussion of the results in the three cases of oxycephaly treated by the King procedure may be grouped under the following headings.

1. Enlargement of the Skull. In each instance, the various measurements of the skull, as illustrated in the case fully detailed, have exhibited an increase following operation.

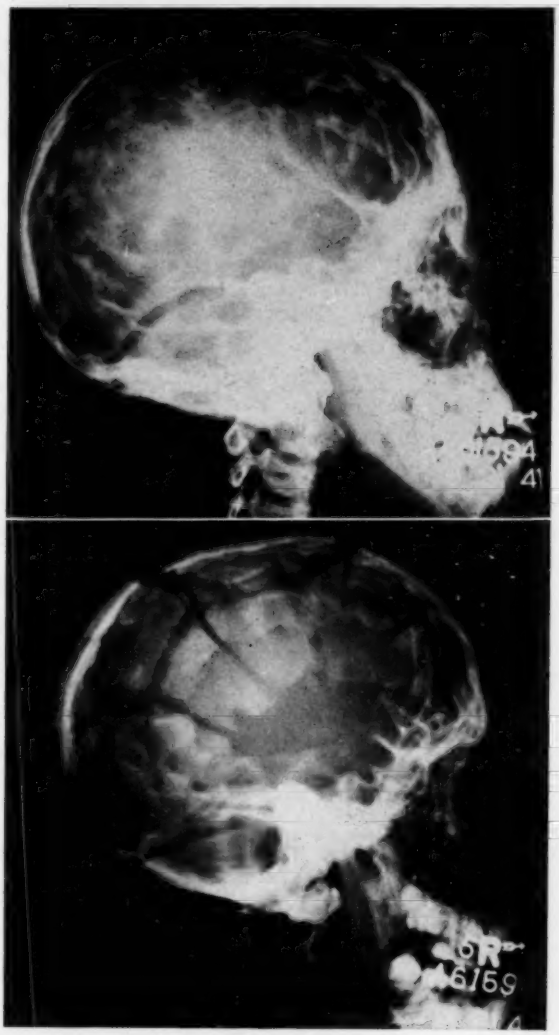


Fig. 3.—*A*, Preoperative and, *B*, postoperative lateral roentgenograms of skull. Note beginning loss of convolutional atrophy in morcellated fragments and early reossification in dural decompression areas.

2. Restoration of Symmetry of Skull. In each instance, the vertex deformity characteristic of oxycephaly has been obliterated and the normal lateral contour of the skull re-established.

3. Relief of Intracranial Pressure. A. At operation, the separation of the morcellated fragments of bone, and the herniation of the dura in the small subtemporal decompression are striking observations, suggesting the immediate expansion of the volume of the cranial vault. In the first patient, thirty months following operation, the digital markings on the inner surface of the skull have disappeared. New bone formation has begun but is not completed. In Cases 1 and 2, ossification is commencing over the area of the bilateral dural decompression, indirectly indicating subsidence of intracranial pressure.

B. In each instance, there has been no further regression in visual acuity. In Cases 2 and 3, in whom visual loss was far advanced, slight but definite improvement has been noted.

C. In each case, the exophthalmus has been reduced but the amount of reduction has not been remarkable. In Case 2, spontaneous subluxation of both eyeballs upon the cheeks had been possible prior to operation and this spectacular feat has now become impossible. With little additional hazard to the patient, resection of the orbital plate might be carried out at the time of morcellation of the skull in extreme instances of exophthalmus.

D. The most striking evidence of relief of an elevated state of intracranial pressure is reflected in a comparative study of electroencephalograms secured before and after morcellation of the skull. Such studies of the electrical activity of the cortex have been completed in two patients and are illustrated in the present case (Fig. 1).

MISCELLANEOUS

In Case 2, preoperative psychometric study revealed a mental status at the level of low-grade moron. Examination one year later suggested improvement, and the examiner felt that this 13-year-old girl could meet the demands of fifth grade schooling. In this child, convulsions had appeared ten months prior to operation; they have remained absent for one year since operation without any other type of anticonvulsant therapy. The final testimony may be added that the parents of these children affirm vigorously that their offspring are improved and are more normal in every respect.

CONCLUSION

Morcellation of the skull as described by King is an ideal procedure for the relief of the symptoms and signs of true and delayed oxycephaly. From our experience with five advanced examples of this particular type of skull deformity, we suggest (1) that morcellation of the skull should be considered as early as the deformity is recognizable in instances of

true oxycephaly, compatible with the surgical hazard incidental to a one-stage or two-stage procedure, and (2) that delayed oxycephaly must be considered in the differential diagnosis of visual loss in children.

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BACILLARY DYSENTERY IN INFANTS AND CHILDREN

Evaluation of Three Media, Sodium Desoxycholate Citrate, S-S, and MacConkey's, for the Isolation of Shigella Paradysenteriae From Stools

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CLINICAL data were presented in a previous paper[1] regarding the value of sulfathiazole in the treatment of dysentery and acute gastroenteritis in infants and children. The present report is an analysis of the efficiency of three media used for the detection of *Shigella paradysenteriae* in the stools of the same patients.

It is obvious to all who have attempted to isolate *S. paradysenteriae* from the stools of children with acute diarrhea that there is great need for a satisfactory medium. Realization of the inefficiency of the best media available for the detection of these specific bacteria led us to compare the value of four media in an early study.[2] The results indicated that Leifsen's sodium desoxycholate citrate medium* was the best, followed by MacConkey's medium,† a good second, eosin methylene blue medium,† a fair third, and Endo's medium,† an inefficient fourth. The best of these four media left much to be desired, since an analysis of the data showed that in only 58 per cent of the Petri dish cultures of this medium was it possible to cultivate recognizable colonies of the bacteria in question.

Three media were used in the present study: Leifsen's desoxycholate citrate medium, MacConkey's medium, and a new medium, S-S,† which has recently become available and was recommended for the isolation of the Shigella and Salmonella groups of bacteria. The patients observed were in two hospitals: thirty-nine in the children's wards of the Cincinnati General Hospital and twenty-seven in the Children's Hospital. The stools from the patients in the General Hospital were cultured in the laboratories of the Children's Hospital Research Foundation, and the stools from the patients in the Children's Hospital were cultured in the laboratories of that hospital. All stools were sent to the laboratory as soon as passed by the patients and were cultured immediately. The data from each laboratory will be considered separately since the procedure was not the same in the two laboratories.

Statistical analyses by Estelle W. Brown and Ruth Blount Bennett, M.D.

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*The Baltimore Biological Laboratory.

†The Difco Company.

STUDIES FROM THE RESEARCH FOUNDATION

Eighty-seven stools from thirty-seven patients with dysentery were studied. Cultures were made at random on duplicate Petri dishes of each of the three media. The cultures from two other patients with dysentery are not considered in this analysis because they were cultured on only two media. The combined results of the three media enabled us to detect *S. paradysenteriae* in each of the eighty-seven stools. These microorganisms were isolated from 389, or 74.5 per cent, of a total of 522 Petri dish cultures. The results for the different media and for duplicate cultures with the same media are shown in Table I. It is seen that 142, or 81.6 per cent, of the cultures with the best medium, S-S, were positive, and only 110, or 63.2 per cent of cultures with the less satisfactory MacConkey's medium were positive. Desoxycholate citrate medium was almost as effective as the S-S medium. Duplicate Petri dish cultures added little information.

TABLE I

POSITIVE CULTURES OBTAINED ON DUPLICATE PETRI DISHES OF THREE CULTURE MEDIA

	MAC CONKEY'S	S-S	DESOXYCHOLATE CITRATE	TOTAL
Plate A	52	72	71	195
Plate B	58	70	66	194
Total	110	142	137	389

TABLE II

ANALYSIS OF VARIANCE (RESEARCH FOUNDATION)

	SUMS OF SQUARES	DEGREES OF FREEDOM	VARIANCE	VALUE OF F	5 PER CENT POINT*
Between media	296.3333	2	148.1667	13.68	9.55
Between duplicate plates of same media	32.5	3	10.8333		
Total	328.8333	5			

F is the ratio of the larger to the smaller variance.

*From Table of Variance Ratios in Fisher, R. A., and Yates, F.: Statistical Tables, Edinburgh, 1938, Oliver & Boyd, Ltd.

The results shown in Table I may be compared statistically by the method of the analysis of variance of Fisher.[3, 4] By this method the variability observed in an experiment is differentiated according to causes or groups of causes. In this experiment variability in numbers of positive cultures observed may be due to, first, differences in efficiency of media and, second, differences between duplicate cultures of the same media. This is a very simple example of a statistical method which is useful in assisting laboratory workers to choose the technique best suited to their problem. We may accept the variability arising from differences between duplicate cultures on the same media as a measure of experimental error. If the variability from this source is sufficiently

large, our confidence in apparent differences between media will be correspondingly small. The form of the analysis of variance for this experiment is shown in Table II. The value referred to as F is the ratio between the variance due to differences between media and that due to differences between duplicate cultures on the same media. A value of F greater than the value of the 5 per cent point given in the next column is commonly accepted as indicating a significant difference. We observe that the differences between media are significant. It may be inferred that the difference lies in the MacConkey's medium which is decidedly inferior to the other two, and this inference is supported by the Chi square test, the results of which are shown in Table III. The extremely small differences between duplicate cultures arise from the fact that, in this series, stools found to be positive on Plate A were almost invariably positive on Plate B. This may be explained by the fact that these duplicate Petri dish cultures were made by a very experienced worker whose sampling of specimen, streaking of material, and recognition of colonies was extremely good. It suggests that in experienced hands more information may be obtained by the use of a single plate of several different media than by the use of an increased number of plates of any one medium.

TABLE III

DIFFERENCES BETWEEN MEDIA, CHI SQUARE TEST

MEDIA	CHI SQUARE	SIGNIFICANCE
S-S and MacConkey's	14.7301	Yes
Desoxycholate and MacConkey's	10.1692	Yes
Desoxycholate and S-S	0.4519	No

Complete data regarding the number of patients, stools, and cultures found positive are presented in Table IV. Here are seen the actual number of patients, stools, and cultures identified by the use of single and duplicate Petri dish cultures with each medium alone and in combination, as well as a summary of the calculated probabilities of finding positive patients, stools, and cultures. Calculations of probability of finding positive patients were based upon the results of the examination of the first stool from each patient. The probabilities of finding positive stools and positive cultures were based upon the total number of stools and cultures examined. This table is included for the benefit of other workers in this field who may wish to compare their results with ours. These figures were computed from our observed data as follows. On MacConkey's medium, for instance, twenty-one patients were found positive with culture A and 24 with culture B. The average of these two, or 22.5, was considered the number which might have been found by the use of a single culture. As the total number of positive patients was thirty-seven, and the number of successes was 22.5, the fraction 22.5/37, or 0.608, gives the probability of success if one Petri dish of

this medium is used. When two Petri dishes of MacConkey's medium were used, 25 out of 37 patients were found positive. The fraction 25/37, or 0.675, gives the probability of success by the use of duplicate cultures. Had the probability for two cultures been calculated from that for a single culture, we should have found a value of 0.846 for p and anticipated a greater number of successes than were actually observed. This discrepancy is, of course, due largely to the fact already referred to, that most patients are found positive by both cultures. If p = the probability of success and q = the probability of failure, then $p + q = 1$ or $q = 1 - p$. In n trials, pn successes and qn failures may be anticipated.

TABLE IV

OBSERVED NUMBERS OF POSITIVE PATIENTS, STOOLS, AND CULTURES AND PROBABILITIES CALCULATED FROM OBSERVED VALUES

COMBINATIONS OF MEDIA	POSITIVE			PROBABILITY OF FINDING POSITIVE		
	PATIENTS	STOOLS	PETRI DISH CULTURES	PATIENTS (P ± S.D.)	STOOLS (P ± S.D.)	PETRI DISH CULTURES (P ± S.D.)
1 MacConkey's	22.5	55	55	0.608 ± 0.080	0.632 ± 0.052	0.632 ± 0.052
2 MacConkey's	25	62	110	0.675 ± 0.079	0.713 ± 0.048	0.632 ± 0.037
1 Desoxycholate	29.5	68.5	68.5	0.797 ± 0.066	0.787 ± 0.044	0.787 ± 0.044
2 Desoxycholate	31	72	137	0.838 ± 0.061	0.828 ± 0.040	0.787 ± 0.031
1 S-S	31	71	71	0.838 ± 0.061	0.816 ± 0.042	0.816 ± 0.042
2 S-S	32	77	142	0.865 ± 0.056	0.885 ± 0.034	0.816 ± 0.029
2 MacConkey's + 2 Desoxycholate	35	78	247	0.946 ± 0.037	0.897 ± 0.033	0.710 ± 0.024
2 S-S + 2 Desoxycholate	35	81	279	0.946 ± 0.037	0.931 ± 0.028	0.802 ± 0.021
2 S-S + 2 MacConkey's	36	84	252	0.973 ± 0.027	0.966 ± 0.019	0.724 ± 0.024
2 MacConkey's + 2 S-S + 2 Desoxycholate	37	87	389	1.000	1.000	0.745 ± 0.019

P = Probability of success.
S.D. = Standard deviation of P.

With such a small series of cases we have relatively large standard deviations. For calculations based upon the results observed with a single culture on MacConkey's medium, we stand a 95 per cent chance of including the exact probability if we consider a range including p ± 2 S.D.; that is, 0.608 ± 0.160. It is, in other words, a twenty to one chance that p for one culture on MacConkey's medium lies between 0.768 and 0.448. For two cultures on MacConkey's medium, the 95 per cent range would be 0.675 ± 0.158 or from 0.833 to 0.517.

Although we see from the observed values in Table IV that all of our patients and stools were found positive by the use of two Petri dish cultures of all three media, the table of probabilities tells us that it is not unreasonable to expect that an equally good result might have been obtained by the use of a smaller number of cultures. It is also important for us to remember that our recognition of dysentery as a disease

depends upon the results of laboratory cultures. These thirty-seven patients were actually known to have dysentery, but it is by no means certain that there were not other patients studied in whom the disease was not recognized.

TABLE V

SELECTIVE ACTION OF MEDIA FOR SONNE AND FLEXNER TYPES OF SHIGELLA PARADYSENTERIAE

MEDIA	SONNE	FLEXNER	TOTAL
MacConkey's	31	79	110
S-S	23	119	142
Desoxycholate citrate	24	113	137
Total	78	311	389

The Sonne type of *S. paradysenteriae* was recovered from 19 of the 87 positive stools and the Flexner type from the remaining 68 stools. One patient showed a mixed infection and is counted in both groups. The selective action of the media for the two types was examined, and the results are presented in Table V. In this small series MacConkey's medium was slightly more efficient in detecting the Sonne type of organism than either the S-S or desoxycholate citrate media. The differences observed in the numbers of positive Petri dish cultures were on the borderline of statistical significance. While the difference is not large, it is sufficient to substantiate the impression that without MacConkey's medium one would fail to identify cases of dysentery caused by the Sonne type of organism. S-S and desoxycholate citrate media were much more efficient than MacConkey's medium in detecting the Flexner type of organism, and these differences were of most decided significance. There was no significant difference in efficiency between S-S and desoxycholate citrate media for either the Sonne or Flexner type of organism. The two media are about equally efficient if numerous suspicious colonies are picked and carefully identified. From a practical standpoint, the S-S medium has an advantage over the desoxycholate citrate medium, since on the former the colonies of Proteus develop brown to black centers earlier, which differentiate them from colonies of *S. paradysenteriae,* thus avoiding needless study of non-dysentery cultures. It is interesting to note that the one patient whose stools contained both Sonne and Flexner types was found positive for Sonne on MacConkey's medium only and for Flexner on S-S and desoxycholate citrate media only.

All eleven patients with Sonne dysentery were detected when each stool was cultured on two Petri dishes of each of the three media or on two Petri dishes each of MacConkey's and desoxycholate citrate media. One patient and one positive stool would have been missed if each stool had been cultured only on two Petri dishes of MacConkey's and two Petri dishes of S-S media. One patient and two positive stools would

have been missed if each specimen had been cultured only on two Petri dishes of MacConkey's medium. Five patients and six positive stools would have been missed if each stool had been cultured on only two Petri dishes of S-S medium. Three patients and four positive stools would have been missed if each specimen had been cultured on only two Petri dishes of desoxycholate citrate medium.

STUDIES FROM THE LABORATORIES OF THE CHILDREN'S HOSPITAL

Each stool was suspended in selenite F enrichment medium, and a 1 to 10 dilution was prepared from each suspension. One Petri dish of each medium was streaked immediately from the original suspension and one from the dilution. At the end of one hour of incubation, two more Petri dishes of each medium were streaked; again, one from the original suspension and one from the dilution. Selenite F enrichment medium was used routinely in this laboratory to assist in the detection of the Eberthella and Salmonella groups of bacteria. In this series fifty-two stools were studied from twenty-seven patients with dysentery. Of a total of 624 cultures, 256, or 41 per cent, were positive for *S. paradysenteriae*. The results for different media and methods are shown in Table VI.

TABLE VI

CULTURES FOUND POSITIVE BY VARIOUS METHODS AND MEDIA

TIME	DILUTION	ALL STOOLS				FIRST STOOL			
		MEDIA			TOTAL POSITIVE CULTURES	MEDIA			TOTAL POSITIVE CULTURES
		MAC.	S-S	DSCY.		MAC.	S-S	DSCY.	
Immediate	Original suspension	16	27	28	71	10	13	15	38
	1:10 dilution	7	20	27	54	3	10	15	28
	Media subtotals	23	47	55	125	13	23	30	66
Incubated 1 hour	Original suspension	23	21	26	70	15	12	17	44
	1:10 dilution	17	17	27	61	8	11	14	33
	Media subtotals	40	38	53	131	23	23	31	77
	Media totals	63	85	108	256	36	46	61	143

It is obvious that in evaluating the results obtained by the use of such a technique there are a number of variables to be considered. The method of Fisher, previously referred to, is at once the simplest and the most accurate method of dealing with the relative error introduced into an experiment by different factors. We have, in this rather elaborate experiment, differences due to the media, the dilution, the incubation period, and, finally, differences due to the interaction of these various factors one with the other. The most reasonable source of variability, which we may use as a yardstick to measure the others, is the interaction of media, dilution, and incubation period. In the analysis shown in Table VII, only first stools are considered.

The analysis of variance shows the two most important factors to be media and dilution. The sodium desoxycholate citrate medium was definitely superior to MacConkey's medium and gave significantly better results than S-S medium. The original suspension gave better results than its 1 to 10 dilution, although this difference was due largely to the fact that with the MacConkey's medium the 1 to 10 dilution gave less positive cultures than the original suspension. The difference in numbers of positive cultures found among Petri dishes streaked immediately and those streaked after the dilution had been incubated for one hour was not significant, but here again the variability observed was due largely to the MacConkey's medium, which yielded much better results when inoculated with the incubated material.

TABLE VII

ANALYSIS OF VARIANCE ON RESULTS OF EXAMINATION OF FIRST STOOLS

	SUMS OF SQUARES	DEGREES OF FREEDOM	VARIANCE	VALUE OF F	5 PER CENT POINT*
Media	79.1667	2	39.5834	25.0006	19.00
Dilution	36.75	1	36.75	23.2110	18.51
Incubation	10.0833	1	10.0833	6.3685	18.51
Interactions					
Media and incubation	15.1667	2	7.5834	4.7896	19.00
Media and dilution	18.50	2	9.25	5.8422	19.00
Incubation and dilution	0.0834	1	0.0834	18.9844	199.5
Media, dilution, and incubation	3.1666	2	1.5833		
Total	162.9167	11			

*From Table of Variance Ratios in Fisher, R. A., and Yates, F.: Statistical Tables, Edinburgh, 1938, Oliver and Boyd, Ltd.

TABLE VIII

STOOLS AND PATIENTS FOUND POSITIVE BY VARIOUS METHODS AND MEDIA

TIME	DILUTION	STOOLS				PATIENTS			
		MEDIA			TOTAL*	MEDIA			TOTAL†
		MAC.	S-S	DSCY.		MAC.	S-S	DSCY.	
Immediate	Original suspension	16	27	28	40	10	13	15	19
	1:10 dilution	7	20	27	34	4	10	15	19
	Media subtotals	17	31	37	45	11	16	19	23
Incubated one hour	Original suspension	23	21	26	35	15	12	17	20
	1:10 dilution	17	17	27	33	8	11	14	18
	Media subtotals*	26	27	35	40	16	17	20	25
	Media totals*	32	40	44	52	18	21	23	27

*Total stool specimens found positive, not numerical totals.
†Total number of patients found positive, not numerical totals.

If the same statistical analysis is made of data on all stools rather than first stools, we find that the experimental error is so reduced that all factors have significance. Differences in numbers of positive cultures obtained by the use of the different media are still the most important source of variability. MacConkey's medium is again the least efficient and most susceptible to variations in the culture technique. Differences in culture methods were of less importance with desoxycholate citrate

and S-S media. S-S medium yielded more positive cultures when the original suspension was streaked immediately, but the numbers are too small to make the differences observed statistically significant.

Table VIII, analogous in form to Table VI, shows the number of stools and patients found positive by various methods. Again it was necessary to use all three media to detect all positive stools and all positive patients. The results presented in these tables are self-explanatory.

CONCLUSIONS

In the laboratory of the Research Foundation, 74.5 per cent of Petri dish cultures from patients known to have dysentery were found positive. The S-S and desoxycholate citrate media were definitely superior to MacConkey's medium in detecting the Flexner type of *S. paradysenteriae;* and MacConkey's medium was slightly more efficient in detecting the Sonne type. When duplicate Petri dish cultures were made, most stools were found to be positive by both cultures and little additional information was gained. There was no significant difference between the results obtained with S-S and desoxycholate citrate medium for either the Flexner or the Sonne type of organism.

In the laboratories of the Children's Hospital, 41 per cent of cultures from patients known to have dysentery were found positive. Regardless of whether Petri dish cultures had been streaked from original suspensions of stools or from 1:10 dilutions of these suspensions, incubated one hour or not incubated, desoxycholate citrate medium yielded significantly more positive cultures than either S-S or MacConkey's medium. S-S medium gave a significantly higher number of positive cultures than MacConkey's medium when the Petri dishes were streaked immediately from both original suspension and dilution. MacConkey's medium was as efficient as S-S medium when the original suspension and the 1:10 dilution were incubated one hour before being streaked on these media.

The efficiency of the three media used in this study for the detection of *S. paradysenteriae* was less than could be desired. Since a higher percentage of positive Petri dish cultures was found when selenite F enrichment medium was not used, it may be that selenite F has an inhibitory effect on the growth of these microorganisms. As selenite F was used on all specimens studied in the laboratories of the Children's Hospital and was not used in the laboratories of the Research Foundation, this factor could not be evaluated.

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RENAL THROMBOSIS IN INFANCY

Report of Two Cases in Male Infants Urologically Examined and Cured by Nephrectomy at Thirteen and Thirty-Three Days of Age

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RENAL thrombosis is an extremely serious disease at any age and in infancy is generally fatal. Massive hematogenous infection is the usual cause when the thrombosis originates in the kidney itself. This variety is designated as primary to distinguish it from secondary thrombosis which develops as an extension of phlebitis of the vena cava, ureteral, ovarian, spermatic, suprarenal, or accessory renal vessels, or follows pronounced inflammation of the renal pedicle when it lies within an acute perirenal suppuration or phlegmon. Secondary thrombosis is more common in adults than infants and children and may develop as a complication of acute focal suppurative nephritis, renal carbuncle, or pyonephrosis. The mortality is always high, and the diagnosis is most difficult to make. The citation of the two cases here reported will indicate frequently observed clinical manifestations of the disease as well as the method of diagnosis and treatment. Unless treatment is prompt and radical, survival is unlikely.

Renal thrombosis is not nearly as rare as the sporadic case reports in the literature would suggest. In 1934, Hepler[1] could collect only forty cases from the literature, thirty of which were clinical observations, and in twenty-two there were definite symptoms referable to the kidney. Eighteen of these patients were less than 10 years old and twelve were less than 1 year of age. In no case had the diagnosis been made with either surgical or post-mortem confirmation. Up to 1936, forty cases of renal thrombosis and infarction in infants and children were observed at autopsy at the Babies' Hospital.[2] Recently, Darenberg, Greenstein, Levy, and Rosenbluth[3] reported five cases of renal thrombosis with infarction complicating diarrhea in the newborn infant from a necropsy series of twenty-five children with infectious diarrhea. Most cases pass unrecognized under the inadequate diagnosis of acute pyelitis or the profound sepsis, or toxemia of intestinal origin causes the urinary tract to be disregarded. In the present communication, two cases of renal thrombosis in the newborn infant are reported. Each was urologically examined and successfully treated by nephrectomy, the infant in Case 1 at 13 days of age and in Case 2 at 33 days of age. The second case is believed unique since apparently it is the first in which the preoperative diagnosis of renal thrombosis was confirmed at operation. Moreover, a careful study of the literature suggests that these are the

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first cases of this condition in which preoperative and postoperative studies of the prothrombin time were made; the value of vitamin K administration was dramatically demonstrated.

ETIOLOGY AND PATHOGENESIS

There is no preference for either side; in half of the cases the disease was bilateral. Sex incidence is about equal; both of the infants here reported are boys. Ileocolitis is the chief predisposing cause of renal thrombosis in the young, but the history in several instances includes measles, diphtheria, cutaneous infections, and particularly omphalitis. In primary thrombosis, hematogenous acute pyelonephritis develops with associated thrombosis of the vessels within the parenchyma, beginning with those of the glomeruli. Here there is often bacterial invasion of the capillary walls with hyaline degeneration of the glomerular structure. Progressively the process involves cortex and medulla, and occasionally thrombotic extensions occur to the other kidney, down the vena cava, iliac, pelvic, spermatic, or ovarian veins, or upward to the pulmonary vascular tree, and even the cerebral sinuses.

Fig. 1.—Right retrograde pyelogram made in Case 1 (male) at 12 days of age. The ureter is well filled and pushed slightly to the midline; the renal pelvis is urographically obliterated by compression due to extreme parenchymal swelling.

In generalized thrombosis the entire kidney is swollen and dark red, purplish or chocolate color (Fig. 1), to which yellowish foci of suppuration may be added. The capsule strips easily, leaving areas of subcapsular hemorrhage and a dark red hemorrhagic cortical surface which

may be studded with miliary abscesses. Only a part of the kidney may be involved (Fig. 2) and the lesion may remain sterile or become infected. In localized thrombosis the involved area stands out sharply in dark red, mahogany, or chocolate-colored relief (Fig. 2).

The microscopic picture is that of glomerular and tubular disintegration and often complete loss of structure (Figs. 3 and 6). To this the histologic elements of inflammation are added and commonly those of infection (Fig. 6). Sometimes bacteria and particularly streptococci can be demonstrated in the thrombotic areas.

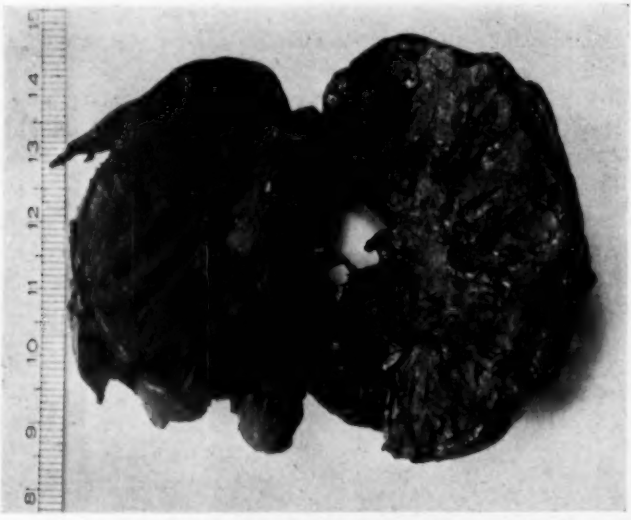
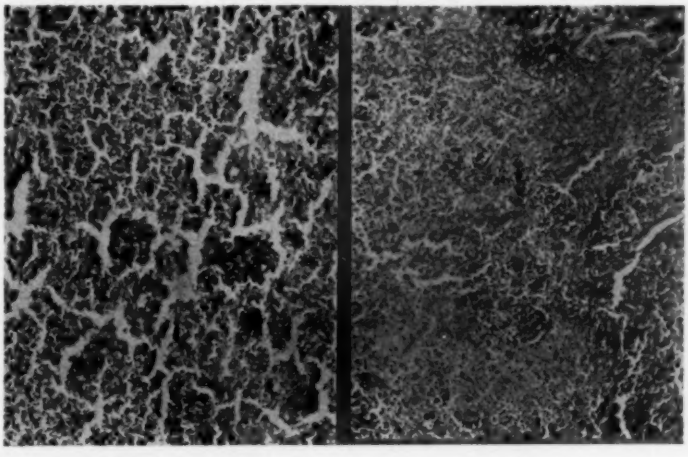


Fig. 2.—Kidney removed at 13 days of age in Case 1. The organ was dark chocolate color and closely resembled a large blood clot. The pelvic vessels were firmly thrombosed.

Several explanations have been advanced for the occurrence of renal thrombosis in infants with ileocolitis. It is true that the resistance of infants to infection of all kinds is extremely low. Blood plasma, volume, and cellular changes consequent to the dehydration of diarrhea may conceivably predispose to thrombus formation and particularly when accompanied by bacteremia in which bacterial embolism engenders local vascular injuries. Today there is no single acceptable explanation. Yet it is notable that in both of our cases, the coagulation and bleeding times were within average normal limits, but in one infant (Case 1) the prothrombin time was doubtless abnormally long prior to the administration of vitamin K because four hours following injection of 1 mg. of vitamin K, the prothrombin time was nineteen seconds (average normal, twenty-five seconds). Lawson[4] states that the oral administration of 1 mg. of vitamin K will restore a low prothrombin level to normal in two to four

hours. In our Case 2, the prothrombin time was one minute, ten seconds prior to the administration of vitamin K but following this medication was reduced to twenty seconds. Parenthetically, this suggests the therapeutic efficacy of vitamin K in these cases of hemorrhagic tendency, but it should be noted that this vitamin is valueless when the prothrombin time is normal.[5]

In about half of the cases of renal thrombosis, there is also infarction which is usually local embolic. Infarction alone is largely a disease of older patients and is usually secondary to vegetative endocarditis. The renal infarction lesion is generally ischemic and pale, but the clinical picture in the two conditions is strikingly similar; treatment and prognosis are identical.



A. *B.*

Fig. 3.—Histology of kidney shown in Fig. 2. *A*, Complete loss of renal architecture consequent to thrombosis; *B*, nearly complete loss of renal architecture. Note the disintegrating remnant of a glomerulus in lower center.

SYMPTOMS

In many cases the clinical picture is that of overwhelming sepsis and toxemia consequent to the major initial condition, whether it be ileocolitis or peripheral infection. Manifestations suggesting renal involvement may be completely masked or may be absent. Yet even in the absence of a palpable tender kidney, the demonstration of albumin, pus, and blood in the urine should arouse more than a passing suspicion.

A sharp pain in the loin accompanied with hematuria, tenderness, and sudden renal enlargement in a child with ileocolitis, at once suggests the diagnosis of renal thrombosis. This occurred in the infants in both of our cases and symptoms referable to the kidney were noted in twenty-two of the thirty reported clinical cases Hepler[1] summarized. The pain

may be local or referred to the bladder, thighs, or genitalia. Vomiting, collapse, constipation or diarrhea, leucocytosis, and fever usually exist, and a marked suppression of urine or even anuria may occur. Although Darenberg and co-workers[3] make the point that symptoms referable to the urinary tract were absent in their five cases, it is possible that strict attention to renal palpation at the time of the acute illness would reveal a swollen kidney or kidneys. In our two cases it was clinically obvious that the infants not only had severe renal pain as well as enlargement but definitely did not want to be moved. Yet in children ill of an overwhelming toxemia, physical examination is usually difficult or unsatisfactory, and the great complexity of presenting symptoms and physical findings may cause the urinary tract to be overlooked. Still, urinalysis of properly collected specimens[6] will hardly fail to give a clue.

The course of renal thrombosis is extremely rapid, almost always ending in death in a few days. The few surviving patients are usually said to have had "acute pyelitis" from which thrombosis must be pathologically differentiated as well as from fulminating pyelonephritis and pyonephrosis.

DIAGNOSIS

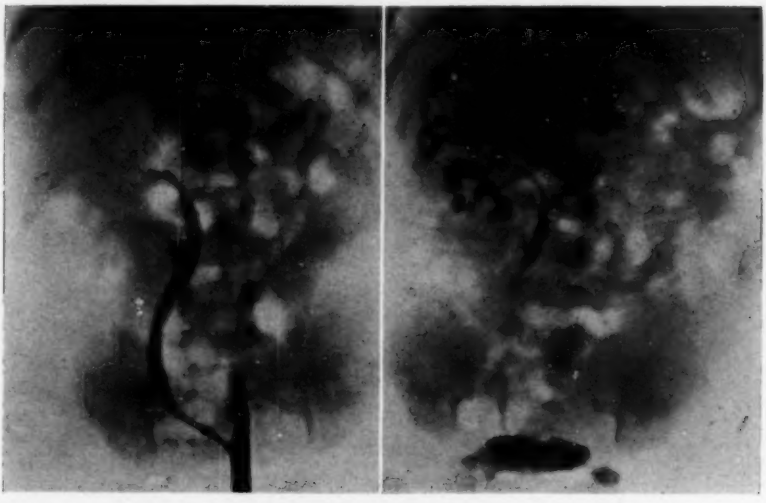
Urinalysis shows blood, albumin, pus, and sometimes pus casts. The urine specimen should be obtained by catheterization in females and preferably so in young males.[6] The history of ileocolitis, the demonstration of renal enlargement, and the urinary findings above indicated at once suggest the diagnosis of renal thrombosis. Each of the infants of the two cases here reported had blood in the stools with constipation in the first instance and normal in the second. Yet it was noted that in each case there was free bleeding on rectal examination, a decidedly abnormal observation in our experiences. Doubtless this was associated with some alteration in the vascular system, and perhaps the same factor caused the curious skin mottling observed in each infant.

In one infant (Case 1) it was thought that renal embryonal adenomyosarcoma (Wilms' tumor) existed, although the persistent temperature and the examination strongly suggested perinephritic abscess.

Despite his desperate condition, the child presenting the above symptoms and findings is entitled to a thorough urologic examination. Excretory urographic studies are likely to be valueless in early infancy[7] and in the presence of abdominal distention, but we feel they are decidedly worth carrying out. In Hepler's patient, a girl 2½ years of age, such studies demonstrated renal enlargement and no function on the diseased side with a normal urogram on the other; renal exploration was completed with nephrectomy.

Cystoscopy can usually be performed without anesthesia in infants. In unilateral thrombosis the divided renal function test is likely to show

no function on that side. Isolateral renal bleeding with diminished or absent function and an enlarged outline are diagnostically suggestive when occurring with the previously described renal syndrome. In our two cases retrograde pyelography was accomplished despite the fact both were infant males. In the first instance the examination was carried out at the age of 12 days and in the second, an unsuccessful attempt was made by an associate on the tenth day and was successfully performed by one of us on the twenty-ninth day. In the first case the retrograde pyelogram showed a good ureteral filling and normal outline with a compression or blotting out of all pelvic markings (Fig. 1). In the second case, essentially the same urēterogram was obtained as in the first, but on further retrograde injection, irregular diffusion of the media throughout the thrombosed organ was evident, as though the injection had been made into a mass of mush (Fig. 4). Still no pelvis was demonstrated. In our first case the preoperative diagnosis rested between perirenal abscess and Wilms' tumor. In the second case and by virtue of our experience in the first, the correct diagnosis was made preoperatively, and to the best of our knowledge is the first time this has been achieved, and certainly in the young.



A. *B.*

Fig. 4.—Right retrograde pyelogram made in Case 2 (male) at 29 days of age. *A*, Good ureteral filling but no pelvic urogram for reason stated under Fig. 1; *B*, urogram following further injection in *A*; no pelvic outlines are distinguishable. There is widespread diffusion of the media through the parenchymal substance, but this does not follow the usual course of pyelovenous backflow or of pelvic overdistention.

In bilateral renal thrombosis, the rapidly fatal course is almost sure to preclude urologic instrumentation, even though it is recognized that urinary tract disease exists.

PROGNOSIS

The prognosis is always exceedingly grave, and over 95 per cent of infants with renal thrombosis will die unless prompt surgical intervention is instituted. Of eight older patients with renal thrombosis treated by nephrectomy,[1] six recovered. Hepler performed nephrectomy in a 2½-year-old girl only to have her die ten days postoperatively of thrombotic extension to the other kidney. Still the chance must be taken. Fortunately both of our patients lived following nephrectomy at 13 and 33 days of age, respectively.

If the child unoperated upon survives, the diagnosis of acute pyelitis is commonly made. If the thrombosed kidney should remain uninfected, a nonfunctioning sclerotic renal atrophy marks the lesion. More often, chronic renal suppuration will demand nephrectomy unless the physician remains satisfied with the diagnosis "chronic pyelitis." As a clinical corollary, the persistence of these conditions might conceivably give rise to hypertension.

TREATMENT

When the renal involvement appears to be unilateral, immediate nephrectomy should be performed (see Prognosis). At nephrectomy in infants, at which age there is practically no perirenal fat, ready mobilization of the inflamed thrombotic kidney may be somewhat difficult. The peritoneum which is like the thinnest cigarette paper is apt to be densely adherent and especially over the anterior renal surface where it is easily broken into. Once penetrated, it is likely to tear widely; in our two cases from the lateral costal border to the pelvis. Approximation of the torn edges is difficult, but great reliance can be placed on a firm closure of the deep fascial layer of the loin.

Preoperative and postoperative supportive treatment largely determines the surgical outcome in infants and children. This includes blood transfusions, combat of acidosis, maintenance of nutrition by gavage, of body heat by external warmth, and of fluid requirements by hypodermoclysis, proctoclysis, or intravenous infusion as indicated, in addition to oral administration. When the prothrombin time is increased, the administration of vitamin K is advised in sufficient amount to restore the prothrombin level to normal. Assuming a short operation under light open drop ether anesthesia, with a minimum of blood loss and manipulative trauma, ultimate surgical success rests upon alert cooperative pediatric management.

CASE REPORTS

CASE 1.—B. B. was a full-term male child born at Mountainside Hospital June 5, 1941, by spontaneous delivery. The family history was irrelevant. He progressed normally until the seventh day when the nurse noted a constipated stool with streaks of bright red blood in it. The skin was mottled. When the child was first seen by one of us (W. F. M.) in the late afternoon of this same day (June 12), the

physical examination was negative except for the presence of a large amount of constipated (heavy putty) stool in the rectum with a few streaks of bright coagulated blood. The body was curved to the right with spasm of the abdominal musculature of the right loin. A firm mass thought to be renal was easily palpated, extending 1.5 to 2 cm. below the umbilical level. The neck seemed stiff. The following day the baby cried when he was picked up or moved. His color was ashen gray and his appearance alarming. Ten cubic centimeters of whole blood was given intramuscularly in each buttock and a fruitless excretory urographic study was made. A lumbar spinal tap was negative. Urinalysis of a specimen casually voided into a test tube revealed a marked trace of albumin and a moderate number of pus cells but was otherwise normal. The blood study at this time revealed the following: red blood cells, 4,620,000; hemoglobin, 88 per cent; white blood cells, 18,800, with 56 per cent polymorphonuclears; lymphocytes, 39 per cent; mononuclears, 4 per cent; myelocytes, 1, and platelets 50,000 (average normal, 250,000). The coagulation time was three minutes, fifty seconds (average normal, seven minutes), the bleeding time was fifty seconds (normal, three and one-half minutes) and the prothrombin time, nineteen seconds (average normal, twenty-five seconds), but it should be noted that this blood was collected four hours and twenty seconds after 1 mg. of vitamin K (synkamen, Parke-Davis) had been given intramuscularly. Subsequently the child received three similar doses (June 18, 19, 22), and the last was given the day following operation at which time there was mild jaundice.

On June 12 the temperature was 101.6° F. and on June 13 increased to 104° F. but slowly regressed during the next four days to 100.6° F., at which time a cystoscopic examination was carried out. Meanwhile the child continued to pass blood in the stool occasionally. There were frequent regurgitations of food. A plain roentgenogram of the body on June 13 showed the lung fields clear, and the supracardiac shadows appeared normal. There was a low mass on the right side of the abdomen, its lower pole extending down to the interspinous line. The contour of the kidney was much too large for this age; there was nothing of diagnostic value in the spine shadow.

Urinalysis on June 16 and 17 showed a marked trace of albumin, faint trace of acetone, many leucocytes, and red cells with coarse granular casts. The red cells persisted in the urine until June 24.

On June 17 at the age of 12 days, cystoscopy and right retrograde pyelography were performed without anesthesia (M. F. C.). By intravenous indigocarmine injection it was determined that a good functioning kidney existed on the left; there was no return of the dye from the right. A 4 F. ureteral catheter was inserted to the right kidney pelvis (10 cm.) and when no specimen was obtained, retrograde pyelography, using 30 per cent diodrast solution, was performed and showed a good filling of the ureter with some median displacement (Fig. 1). There was no pelvic shadow in the urogram. A provisional diagnosis of perinephritic abscess or Wilms' tumor was made and renal exploration advised. The child was given 90 c.c. of whole blood by direct transfusion, and on June 18 at the age of 13 days, right nephrectomy was performed under open-drop ether anesthesia.

At operation (M. F. C.) the kidney was found to be twice normal size and presented a blue-black appearance (Fig. 2). The perirenal structures were densely adherent, particularly the anterior peritoneum, which was badly lacerated in mobilizing the kidney. The kidney was loosened from its bed and the ureter divided between ligatures in the usual manner, but with the maneuver to place a clamp on the renal pedicle, the organ spontaneously dropped off in the hand. Further attempt to clamp the pedicle revealed it to be cheeselike, and since it seemed unlikely to bleed, ligation was omitted. The peritoneum was closed and the loin wound was sutured, leaving two small Penrose drains in the retroperitoneal space.

Postoperatively an indwelling nasogastric tube was maintained with gavage feedings; fluids were given through the tube and normal saline-5 per cent glucose solution was administered both subcutaneously and intravenously (average of 750 c.c. per day total fluid intake). Because of marked anemia, three transfusions of 90 c.c. of whole blood and 10 c.c. of saline were given.

On June 19 the red blood cell count was 2,960,000, with 60 per cent hemoglobin, and white blood cells, 30,400. On June 21 after transfusion the red blood cell count increased to 3,500,000, with 68 per cent hemoglobin, but it dropped two days later, increasing following another transfusion to 3,900,000, with 76 per cent hemoglobin. On the day of discharge, the red blood cell count was 3,500,000, with 68 per cent hemoglobin, white blood cells, 12,700, with 36 per cent polymorphonuclear leucocytes.

The patient was discharged on July 1. Five months postoperatively the child's development, blood count, and urine were normal.

Pathology Report (Dr. M. J. Fein).—

Macroscopic Examination: The kidney measures 7 by 3 cm., the surface is lobulated, chocolate brown in color and roughened. On section, the entire kidney substance is occupied by blood which is coagulated in some areas and softened in others.

Microscopic Examination: Throughout these sections, the histopathologic characteristics of this kidney are entirely replaced by large areas of hemorrhages with considerable amount of blood pigment. The remaining smaller blood vessels show thrombosis.

Diagnosis: Thrombosis of the kidney.

CASE 2.—B. P. was a male infant born at Mountainside Hospital July 19, 1941, at full term by spontaneous delivery. The family history was irrelevant. He progressed normally until the fifth day (July 24), at which time he vomited, passed bloody urine, and was slightly cyanosed with a mottled appearance of the skin. The physical examination (W. F. M.) revealed tenseness but no rigidity of the neck. There was moderate spasm of the muscles of the right abdomen and loin with resistance to abduction. The right kidney was palpable 3 cm. below the level of the umbilicus; it was hard and smooth. The urine continued to show blood clots, and there was projectile vomiting with small streaks of red blood on the diapers. Urinalysis at this time showed a marked trace of albumin with a large number of leucocytes and innumerable red blood cells. The patient cried as if in pain and held himself rigid when picked up; he apparently disliked being moved. The blood count at the time showed red blood cells, 5,900,000; hemoglobin, 118 per cent; white blood cells, 29,200; polymorphonuclears, 71 per cent; lymphocytes, 23 per cent; mononuclears, 4 per cent; and platelets, 200,000. The coagulation time was three minutes, forty-five seconds; bleeding time, forty-five seconds; and prothrombin time, one minute, ten seconds (normal, twenty-five seconds). It was felt that the high red cell count was both neonatal and the result of dehydration. Two days later the hemoglobin was 92 per cent. The following day (July 25) there was a severe gastrointestinal upset with vomiting which was treated by gavage feedings. An excretory urogram was unsatisfactory, there being no urographic shadows except in the bladder. The hematuria persisted. In the absence of one of us, a cystoscopy was unsuccessfully attempted by an associate. The child continued to have gastrointestinal disturbances with vomiting and abdominal distention which were symptomatically treated with Levine nasogastric tube, gavage, oxygen, whole blood injections into the buttocks, and transfusions. Vitamin K (1 mg. synkamen) was given intramuscularly on five occasions (July 24, 25, August 2, 13, 14). Gavage was discontinued on July 28, and the child was definitely improved. Slight diminution

in the size of the right loin mass was observed. Yet he continued to have fever and periodic hematuria. On August 13 progress was satisfactory and the temperature normal; he took the formula well and gained. There was still blood in the urine and some regurgitation. The right kidney persisted large but was definitely smaller than at the height of the illness. When first seen August 17 by one of us (M. F. C.), it was thought that the child probably had a congenital hydronephrosis which had become acutely infected and enlarged but with spontaneous drainage had regressed in size and nonurinary symptoms had correspondingly subsided. A recheck excretory urographic study was made with roentgenographic exposures every two minutes for ten minutes following injection of 9 c.c. of diodrast, but these were unsatisfactory and indicated only the large right loin mass. The same day (patient 29 days old) a cystoscopic examination was made (M. F. C.) without anesthesia, and by indigocarmine intravenously the left kidney was determined to be functioning normally. There was no return of the dye from the right kidney in a fifteen-minute observation. Culture of the bladder urine showed *Bacillus coli* infection. A 4 F. catheter was passed to the right kidney pelvis; no specimen was obtained.

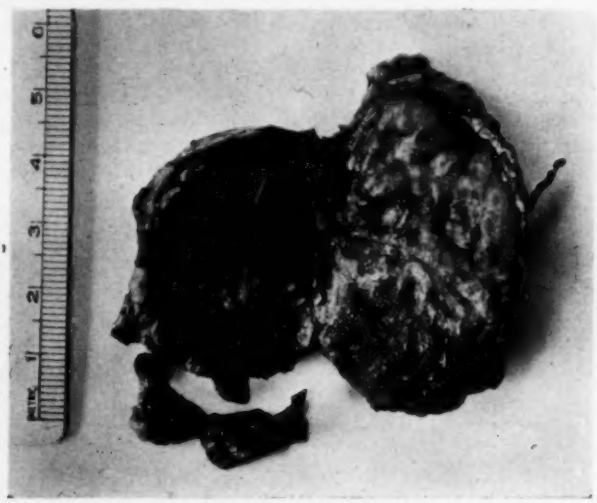


Fig. 5.—Kidney removed at 33 days of age in Case 2. The thrombosis involves the lower portion of the organ; some friable pieces broke off and were lost. The upper half of the kidney was riddled with suppurative areas, and the pelvis was filled with a thick greenish pus which on culture showed *B. pyocyaneus*.

A retrograde pyelogram was then made, injecting first 2 c.c. of 30 per cent diodrast solution. This outlined the ureter well but showed no pelvic shadow (Fig. 4*A*). Further injection showed an irregular blotchy diffusion of the media throughout the kidney which suggested extravasation through spongy tissue (Fig. 4*B*) rather than pyelovenous backflow or the usual type of diffusion of pyelographic media due to overinjection. By virtue of our recent experience with Case 1 and the striking clinical and urographic similarity, a preoperative diagnosis of renal thrombosis was made and four days later nephrectomy was performed; the boy was 33 days old (August 21, 1941).

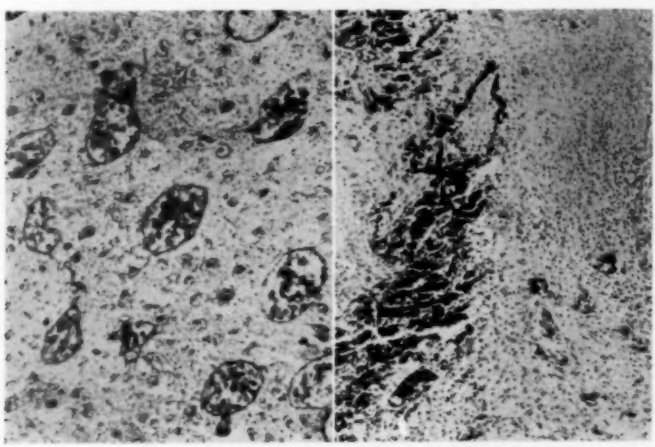
The operation was carried out as in Case 1 under open-drop ether anesthesia. The kidney was enlarged nearly twice normal size, and the lower half appeared bluish-black; the upper half was pale with scattered small cortical abscesses (Fig. 5).

There were dense perirenal adhesions throughout and particularly over the anterior renal surface to which the peritoneum was firmly attached. In mobilizing the kidney, the peritoneum was rather widely torn posteriorly but was closed with a continuous suture. The ureter was divided between ligatures, and the kidney was removed in the usual manner, using two clamps on the pedicle with a double transfixion suture. The loin wound was closed, leaving two small Penrose drains in the retroperitoneal fossa.

Postoperative convalescence was moderately stormy, but nutrition was maintained by use of an indwelling nasogastric tube which served not only for gavage feeding, but also for gastrointestinal decompression. Transfusions were given and several hypodermoclyses. The prothrombin time one day postoperatively was twenty seconds. One week postoperatively the hemoglobin was 80 per cent; red blood cells, 4,500,000; white blood cells, 25,000 (polymorphonuclears, 80 per cent, lymphocytes 15 per cent, eosinophiles, 5 per cent); prothrombin time, twenty-eight seconds; the urinalysis disclosed a faint trace of albumin, scattered leucocytes, and an occasional red blood cell. The child left the hospital in good condition on September 5 with only a small amount of exudate coming from the posterior angle of the wound where the drain had been. Subsequent development and function have been normal.

Pathology Report (Dr. M. J. Fein).—

Macroscopic Examination: Kidney measures 5 × 2½ × 2 cm., the surface is nodular, partially covered with blood; it is lobulated. On section, the lower portion has a hemorrhagic area present which measures about 3 × 2½ cm. The rest of the kidney substance is mottled in appearance, rather irregular, and contains some brownish yellow spots. The cortical portions of this kidney are indistinct.



A. *B.*

Fig. 6.—Histology in Case 2. *A*, Widespread cortical destruction with disintegrating glomeruli; *B*, section taken at junction of black thrombotic area (left) and suppurative area (right). Complete loss of renal architecture.

Microscopic Examination: Sections taken from the hemorrhagic area show considerable amount of necrosis of the kidney substance and only mere shadows of the glomeruli and tubules are seen. The blood vessels are dilated and engorged with red blood cells, and some are thrombosed. The remainder of the kidney tissue shows a marked infiltration with polymorphonuclear leucocytes with pyknotic nuclei, serum exudate, and some hemorrhages in the interstitium.

Diagnosis.—Thrombosis of the kidney (with an acute suppurative nephritis).

SUMMARY AND CONCLUSION

Renal thrombosis in infants and children is an exceedingly grave condition and terminates fatally in practically every case not promptly treated surgically. In infants, ileocolitis is the chief predisposing cause; the initial renal lesion in most cases is a massive hematogenous acute pyelonephritis. The precise factor or factors engendering the early intrarenal lesion are unknown. In Case 2 the prothrombin level was strikingly low (one minute, ten seconds) and, as pointed out in the text, there is reason to believe the level was correspondingly low in Case 1. Yet in each instance a high prothrombin level was rapidly achieved by the administration of vitamin K. The clinical manifestations have been presented and in a large portion of the cases adequate urologic study should establish the urgent surgical nature of the condition; in some the correct diagnosis will be made preoperatively. When (1) the disease is unilateral, (2) the child is not hopelessly septic, and (3) prompt nephrectomy is employed, about 75 per cent may be expected to survive. In the two male infants here reported, cystoscopy, divided renal function tests, and retrograde pyelography were carried out in the early days of life and shortly following the onset of the disease. Both were cured by nephrectomy.

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140 EAST 54TH STREET
180 WALNUT STREET

HUMAN MILK TECHNOLOGY

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THE standards for directories for mothers' milk prepared by MacPherson and Talbot[1] and published in 1939 presented the methods then in use at the Boston Directory for the selection of mothers, the collection of their milk, its pasteurization, preservation, and distribution. It had been found by considerable experience that by the use of those standard methods a hygienic produet was obtained with efficiency and dispensed without possibility of deterioration or contamination. The Standards, or others applicable to all communities, such as are now being developed by the American Academy of Pediatries and shortly to be published, may well be made the basis of any legal regulations governing the commercial sale of human milk, should the application of such legislation ever be deemed necessary. Besides the more or less administrative aspects of human milk supply to which they refer, there are the more technologic procedures which have been investigated and in certain instances adopted as part of the operation of the Boston Directory. With each new consideration of this sort, difficulty has been encountered in searching out and surveying a rather scattered literature. This fact, and the opportunity for discussing a few procedures on the basis of experience with them, has prompted the present article. It is concerned primarily with (1) methods of identification and tests for adulteration of human milk; (2) pasteurization and tests of pasteurization; (3) methods of preservation; and (4) the effect of some of these procedures on the food and vitamin values of the milk.

IDENTIFICATION

It is obvious that in organizations to which lactating women come for periodic pumping or expression of milk, questions of adulteration will hardly arise. If, on the other hand, the milk is expressed or pumped by the women at home and kept there for collection at daily intervals, these questions will arise often enough so that some fairly simple means of ruling out adulteration is necessary. The first need is to determine adulteration with water, the second, to ascertain the presence of milk from another species. Of these, the former is much the more difficult, for the addition of water to milk is not easily detected. Methods which depend upon alterations of the freezing point and refractometric analysis[2] are sometimes used in the dairy industry but present obvious difficulties. Variations in total solids or specific gravity will not, by themselves, be very helpful in a physical system whose water content is normally from 85 to 90 per cent, since much more water may be added

From the Department of Pediatrics, Harvard Medical School, and the Directory for Mother's Milk, Inc., Boston, Mass.

with a relatively slight change in proportions resulting. For example, the adulteration of a quart of milk having an 85 per cent water content by the addition of an additional pint of water will raise the percentage of water in the total only to 90 per cent. The specific gravity would be recognizably altered by such a procedure, but this is also affected by variations in the fat content of the milk. Because milk fat is lighter than water, increases in the fat content will lower the specific gravity; thus a woman may send in milk which has a low specific gravity not because it contains too much water but because it contains an excess of one of its normal solid components. Ström[3] has found that a normal woman's milk may vary in fat content from 2.2 to 8.8 per cent in samples taken on the same day, indeed only a few hours apart, so that any determinations of specific gravity are of little value as evidence of milk dilution unless the fat content of the sample is known. This can best be learned by the standard Babcock test,[2] a procedure in regular use in dairy laboratories.*

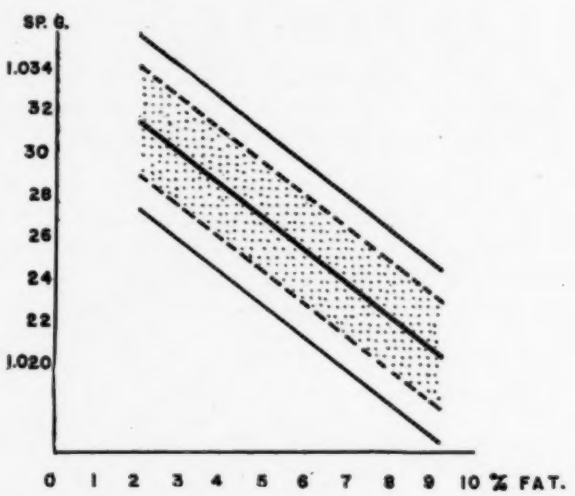

Fig. 1.—Chart devised by Ström[3] to indicate adulteration of human milk with water. The center line represents the mean of specific gravity and fat content measurements in seventy-five samples of normal human milk, most of which resulted in points falling within the shaded area. Points outside this area, if still within the solid lines, are also compatible with normal variations, although they raise suspicion of dilution. Any milk whose specific gravity and fat content measurements give a point outside the solid lines is certainly diluted with water.

With the fat content thus determined and the specific gravity of the milk measured by a milk hygrometer (lactometer), one can plot a point on the chart devised by Ström[3] (Fig. 1) and determine whether it falls within the area of normal variation or outside this in the region

*So routine a procedure is this in such laboratories and so standardized is the equipment required that much time and effort may be spared if dubious samples of breast milk can be analyzed by one of these institutions.

which signifies a diluted milk. It becomes clear from the chart that in milk which originally had a high specific gravity and a moderate fat content (i.e., S.G. 1.032, fat 4 per cent), a considerable dilution with water could be practiced without detection; in fact, water might be added until the specific gravity is markedly lowered and still the chart would show a point within the bounds of normal variation. Actually Ström has calculated that in certain milks a 32 per cent addition of water would still result in fat and specific gravity within the range of normal. On the other hand, one can understand from the chart how in milk with a 4 per cent fat content and an original specific gravity of 1.028 a very slight dilution would be discovered.

In the dairy industry, the test for adulteration of cow's milk by the addition of water is usually performed by determining the fat percentage and then applying the formula:[4]

$$\frac{\text{Lactometer}^*}{4} + 1.2 \text{ fat} = \text{per cent of total solids}$$

Per cent of total solids − per cent of fat = per cent of solids not fat

If the figure for solids not fat be less than 8 per cent, water dilution is suspected; if less than 7.7 per cent, water dilution is almost certain. The same formula could be applied to human milk, and under some circumstances might give a more accurate check on water dilution than the use of Ström's diagram. Both methods of course require the determination of fat content.

More numerous procedures have been advocated for determining adulteration of human milk by the addition of cow's milk. Those with which we have had experience are discussed below, while several others mentioned are reviewed in the paper by Gnosspelius.[5]

Since the average hydrogen-ion concentration of human milk gives a pH of about 7.0 or slightly above, and that of cow's milk about 6.7, it is natural that several reactions based upon this difference should have been advocated. The range of pH normally encountered in human milk extends, however, from 6.9 to 7.4, and that of cow's milk from 6.5 to 7.2,[6] so that a wide degree of overlapping is possible. The nile blue sulfate test, modified from Bauer's method,[7] is one of those dependent upon differences of acidity; it is performed very simply by mixing equal parts of the milk to be tested and a 0.25 per cent solution of nile blue sulfate dye in water. In the presence of human milk, the mixture in the test tube assumes a rosy pink or magenta color, but if cow's milk is present, the resultant color is a dull purplish blue. In the past this reaction was a standard procedure at the Directory, even though samples known to be human milk sometimes gave a color practically indistinguishable from the blue produced by cow's milk. Studies carried out with the help of Dr. Eric Peters showed that when such confusing specimens were boiled the color changed toward the pink one characteristic of human milk, while this

*In this sense, lactometer means the last two figures of the specific gravity reading, usually about 32 (i.e. S.G. = 1.032).

did not occur on heating those blue mixtures of known cow's milk and dye. The test performed with this modification, and done by mixing one drop of milk and one of dye upon a white glass plate, seemed fairly rapid, economical of milk, and reasonably accurate. However, the reaction apparently depends at least in part on some unusual characteristic of certain stocks of nile blue sulfate, since after the international situation made it no longer possible to get the dye from Germany, it was discovered that the domestic material did not give reliable color changes.

Another dye test advocated by Solé[8] consists of adding to a small sample of milk an equal portion of saturated solution of hematoxylin, such as is used in histologic work. A purple color, deepening upon standing, is to be expected in the case of human milk, while a bright yellow-red color should appear with cow's milk. In a series of determinations carried out with the assistance of Dr. Peters, the end-point of this test was found to be less clear and the number of confusing reactions somewhat more frequent than had been encountered with the nile blue sulfate dye.

Difference in hydrogen-ion concentration is also the basis of the neutral red reaction, advocated by Moro[9] and mentioned by Gnosspelius[5] but not tried in our laboratory. It is said to fail in detecting cow's milk unless it is present in more than 10 per cent concentration. Jacobi[10] advocated a color reaction supposedly due to differences in the type of casein, because of which a purple color appears when concentrated sulfuric acid is added to cow's milk but a brown color when the milk is human. Another test based on casein differences has been described by Zimmermann[11] and modified by Urbach,[12] but since it requires forty-eight hours for the complete precipitation of clotted casein from cow's milk (upon the addition of dilute acid), it has not aroused our interest enough to stimulate its experimental use. The light refraction method of Kapeller and Gottfried,[13] as described by Gnosspelius, requires expensive and complicated apparatus.

Our interest was for some time attracted by the papers of Kayser[14] who advocated a different sort of color reaction, appearing when the milk is seen under ultra-violet illumination. Most samples of human milk assume a blue or violet fluorescence under such light, while cow's milk as a rule takes on a flaxen yellow shade. The method was found to be quick and easy of application in our laboratory, but there were usually a few specimens in every morning's collection of breast milk which gave a more or less yellow color. Therefore, a large number of specimens from nursing mothers in the Boston Lying-In Hospital were examined, but even in these proved samples of human milk the yellow color occasionally appeared. We were never able to learn what interfering substance caused the peculiar reactions. Kayser[15] later suggested that they followed the addition of liver to the maternal diet and might indicate the presence of lactoflavine, but that did not always prove to be the case in our experience.

Such biologic tests that are based on anaphylactic shock and complement fixation are complicated and time-consuming. The injection of milk from the cow into the blood stream of another species (rabbit) produces precipitins, which are, according to Gnosspelius, primarily due to the casein portion of the milk protein though also to the less specific lactalbumin and lactoglobulin fractions. Since the caseins of human and cow's milk have certain fundamental differences, rabbit serum containing the precipitins so induced will react specifically with cow's milk to form a definite precipitate not appearing when such serum is mixed with milk from any other, such as the human species. The titer of rabbit serum, and thus the sensitivity of the test, can be raised in direct proportion to the number of times the rabbit is injected with milk. On the basis of some experimentation, Gnosspelius advised the use of five inoculations of 5 c.c. of cow's milk each, on alternate days, after which the serum is tested for its titer; if satisfactory, the rabbit is bled and the serum mixed with a preservative and stored for use. Serum so prepared by Gnosspelius and mixed on a glass slide with an equal amount of milk gave a definite and grossly visible precipitate formation in the presence of as little as a 5 per cent dilution with cow's milk. Since casein is thermostable, the reaction is also given with milk that has been boiled. The caseins are so consistently and definitely specific that the mother, even by consuming large quantities of cow's milk, cannot secrete breast milk which gives a false positive reaction.

This test has been found very satisfactory in recent use at the Directory in Boston. Serum from rabbits given only three intravenous inoculations on alternate days has been of such strength that when one drop of it is mixed with a drop of breast milk adulterated with 20 per cent cow's milk, a precipitate forms, and with more sensitizing doses a higher titer is produced. One rabbit will yield up to 50 c.c. of serum; for such an amount the addition of 0.5 c.c. of a 1 per cent aqueous solution of neutral acriflavine is a satisfactory preservative, after which the serum may be stored in sealed capillary tubes of about 15 cm. in length. One such tube, containing 0.2 c.c. of serum or less, can be used for testing some twenty samples of milk if the drops delivered from it are not too large. Precipitation, when it occurs, can be observed easily if the mixture with milk is made with some stirring and the glass plate on which this is done is obliquely illuminated from slightly below but held with a dark background directly behind it. It is well to verify this by testing one drop of known cow's milk each time human milk is so examined. It is obvious that this test will not detect the presence of milk from some other species, such as that from the goat, although of course a serum for that purpose could be made.

It may also be said from a practical standpoint that the adulteration of breast milk with cow's milk, if practiced for economic gain by a woman selling her milk, might well be detected or at least suspected from the bacteria count in the adulterated portions. It would be diffi-

cult to dilute with cow's milk without raising the bacteria count at the same time unless such an expensive grade of milk was used for the adulterant that the fraud would not be economically worth attempting.

PASTEURIZATION

Milk collected under satisfactory home conditions and even that pumped or expressed under the most ideal conditions at dispensaries may contain a certain number of bacteria, the count being from 500 to 3000 colonies per cubic centimeter in that kept on ice in the home for daily collection.[1] So rapidly may organisms increase thereafter that some form of sterilization is required even though the milk be dispensed at once. For this, ordinary boiling may be used as an expedient. In the 1939 Standards, MacPherson and Talbot[1] advise pasteurization at between 140° and 145° F. for thirty minutes, a process which has proved satisfactory during many years of operation, since immediately thereafter the milk is sterile and if kept properly chilled will remain so for at least forty-eight hours. In Massachusetts the legal standard for the pasteurization of cow's milk has been decreed as a temperature of 142° F. or above, maintained for at least thirty minutes; but the so-called "flash" pasteurization of 161° F. for sixteen seconds is also legal and might be applied to human milk.

The bacteria count constitutes a fair check on the efficacy of the pasteurization process. Another check is the so-called phosphatase test as devised by Kay and Graham[16] and later improved and simplified by Scharer.[17] The reaction depends upon the phosphomono-esterase naturally present in raw milk and its almost complete destruction at the temperature of pasteurization. At the Directory in Boston the efficacy of pasteurization is checked by this method by testing a few random samples from the pasteurizer every two weeks.*

PRESERVATION

The difficulties of meeting a sudden demand for breast milk and the advantages of saving a temporarily excessive supply have called forth various methods of preservation. The dairy industry has met the same problem by condensation with sugar, by partial evaporation, and by complete drying to a powder. There is no reason why these same processes cannot be applied to the handling of human milk, but a search for practical and simple procedures using more easily available apparatus has led to experimentation with and sometimes adoption of other methods. Methods such as the so-called "lyophilization"[18] or drying from the frozen state, which are increasingly used for the preservation of sera and other biologic materials, are being studied as possible means of milk preservation. In many cities some form of apparatus for this purpose

*A convenient set of apparatus for the test can be obtained from the Applied Research Institute, 15 West 34th Street, New York, N. Y.

is available at one or more medical centers; by its use, milk in units of 8 ounces or more can be reduced to a dry or somewhat oily powder or cake in a process requiring from twelve to twenty-four hours. The milk can then either be stored in the original containers from which evaporation took place or the powder from several of these containers can be scraped out under sterile precautions and combined in a single larger one. The volume of the original milk must be known so that proper dilution or reconstitution for use can be performed by the addition of the proper amount of sterile distilled water.

In our experience with a few samples so prepared for us by Dr. S. H. Armstrong,* the reconstituted milk formed a rather poor emulsion, with collection of the fat into larger, coarser globules than in the unprocessed milk. This effect, although quite obvious, was less noticeable in samples of human milk than in those of cow's milk and did not seem to disturb the digestion of an infant to whom 16 ounces of such human milk was fed. The taste of cow's milk thus dried and then reconstituted was abnormal. Possibly if human milk were homogenized by forcing it through a very fine aperture before freezing and drying processes were applied, this fat separation might be prevented. Folsom,[19] working at the Memorial Hospital in New York, has noted a tendency for cow's milk (and particularly cream) desiccated from the frozen state to become rancid during storage unless air is kept from it. For this reason and others it might well be preferable to keep the dried powder in vacuum in the original container from which its water portion was drawn off. This of course requires the expense of larger receptacles and ones which may be sealed off, as by the melting of a narrow neck, to preserve pressure conditions within. On the whole, it appears that any such desiccating process, whether it be of the "lyophile,"[18] "cryochem,"[20] or "desivac"[21] type, will probably prove too expensive for the regular processing of breast milk. All such methods of course do offer the distinct advantage of dispensing with specially chilled space for the product during storage or transportation.

Breast milk may be processed in several ways if it is to be held thereafter near or at subfreezing temperatures. One simple method was that described in 1933 by Broadhurst and Duncan.[22] The milk, triply pasteurized by heating to 175° F. for thirty minutes on three successive days, could then be kept in a refrigerated (but not frozen) state two years or longer without bacteriologic or chemical change being noted, and, as Scheuer and Duncan[23] showed, could thereafter be successfully fed to small infants.

During a long series of studies carried on at the Directory for Mother's Milk between 1922 and 1933, Emerson and others,[24] after first reporting that contemporary processes for drying breast milk had not proved satisfactory, then described a method for the solidification of milk by quick freezing.[24f] In that form it could be held at subfreezing

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temperatures with suspension of bacterial or chemical activity more or less indefinitely and thawed to a state entirely similar to its prefrozen condition. This freezing procedure* attained its rapidity of action by virtue of the small size of units frozen and by the use of cakes of solidified carbon dioxide (dry ice) to transmit very low temperatures to the milk as poured into the shallow depressions of an aluminum mold. The small cakes or wafers of frozen milk (each one about 10 c.c. in volume) after being taken from the mold could be collected in sterile glass jars, 8 ounces of milk occupying a 16-ounce jar, because of the loose packing of the wafers. This process proved entirely successful and was in regular use at this and other mother's milk stations for eight or more years, during which time the only modifications of the process involved have been changes in the temperature of the storage space. It was thought at first that an important amount of slow bacterial multiplication might be avoided if the frozen milk were held at an extremely low temperature, and for this reason a storage at −26° C. (−15° F.) was formerly advocated. Through the kindness and interest of Prof. B. E. Proctor, of the Massachusetts Institute of Technology, studies were made in 1937 by Bertrand Bennison of that institution which indicated that a holding temperature of −12° C. (10° F.) could be considered safe and satisfactory. The recent development of frozen food lockers in which family provisions may be kept has made excellent holding space available in certain cities. The Variety Club Mother's Milk Bank in Memphis, Tenn., keeps some 2,400 ounces of frozen milk in this way at a temperature of between −18° and −23° C. (0° to −10° F.).

Since the quick-freezing method has the drawback of requiring considerable time and handling as well as excessive storage space because the frozen units store so loosely, a number of experiments have been carried out at the Directory to determine whether milk might be frozen in larger units, perhaps with somewhat less rapidity but nevertheless quickly enough so that its digestibility on thawing might be unimpaired. So general is the impression that milk frozen slowly is indigestible[6] that every attempt was made to keep the process as rapid as possible. Thus it was found that fourteen minutes would suffice for the freezing of milk in an 8-ounce unit if the process were carried out in a dry ice-acetone bath at a temperature of −70° C. (−94° F.), the milk being first sealed in a tin can or a pyrex bottle and then immersed in such a bath.[25] At the suggestion of Professor Proctor and with the cooperation of Mr. David Greenlie, it was also found possible to freeze breast milk in conveniently rectangular 8-ounce bricks by pouring it into latex or "cryovac" bags† and setting these in a metal mold surrounded by the dry ice-acetone mixture. All of these preparations, even though their freezing required perhaps five times as long as did the original process, re-

*The Borden Company of New York City controls the patent on this freezing process and the molds used.

†Furnished by the Dewey and Almy Chemical Co.

sulted in milk which was of satisfactory appearance and bacteria content upon thawing, and which was fed to a number of premature infants with complete success.

In 1934 a brief and not very detailed article by Stern and Lieberman[26] announced that those authors had fed a number of premature infants with breast milk which had apparently been frozen in the ice compartment of an ordinary electric refrigerator, and in 1940 we learned that at the University Hospital at Iowa City it was the practice to preserve breast milk by freezing it comparatively slowly at about –7° C. (18° F.) in the hardening compartment of an ice cream machine. On the assurance of Dr. E. D. Plass that the product had been fed with success to premature and mature newborn infants, the same process was instituted at the Boston Directory. At the temperature used at the University of Iowa Hospital, it was found that 8- or 16-ounce bottles of breast milk became solidly frozen in from thirty to sixty minutes. The milk upon thawing presented an emulsion of fat not quite so fine as that of the original fluid, the fat globules being larger when examined microscopically. There was also a slight tendency for the protein to separate in a few fine threads of curd, but both of these manifestations became less noticeable when the milk was warmed for feeding. The preservation procedure is particularly simple if the laboratory maintains a cold cabinet or locker for holding frozen milk, since any surplus amount of pasteurized milk may simply be left in a sterile (Mason) jar at this holding temperature until frozen. To prevent breakage of glass, it is wise to cover the jar with sterile gauze during the process or to set the glass lid on loosely. After the milk is solidified, the jar can be sealed with its glass lid and rubber ring, wrapped, labeled, and replaced in the storage. Thus far, more than a thousand ounces have been preserved in this way at the Boston Directory to be thawed and fed to small premature infants with entirely satisfactory results, even though the freezing time is ten to twenty times that which the earlier workers strove to achieve. Besides the experience at Iowa City an article[27] has recently been published describing a similar refrigerator technique for preservation of breast milk that is in satisfactory operation at the Presbyterian Hospital in Chicago.

THE EFFECTS OF PROCESSING ON FOOD VALUE

As shown by the practical tests of successful utilization by small infants, there is no evidence that the protein, carbohydrate, or fat content of milk is altered importantly by pasteurization or by quick freezing.[24g] Although slowly frozen cow's milk is traditionally indigestible by the human infant, there is strikingly little in the way of controlled observation upon that point in the literature of pediatrics. Two studies of the effect of feeding frozen milk to animals have been found in the dairy journals. In one,[28] evaporated milk allowed to congeal at –5° F. and held at that temperature for several months was melted and fed to young

rats. During a twelve-week period on this diet, the rats gained as well as did a control group. In another series of experiments by Munkwitz, Berry, and Boyer,[29] pasteurized cow's milk, frozen slowly, thawed, and fed to rats was shown to be well tolerated. Thus there seems to be no positive evidence available to prove that freezing disturbs the digestibility or nutritional value of milk.

"All the known vitamins are present in breast milk, the quantity being greatly influenced by the intake of the mother."[6] That at least one of these substances, vitamin C, is more or less destroyed by the temperatures of pasteurization is well known. Since breast milk is usually pasteurized before being preserved by freezing, the question of the effect of cold preserving processes on this vitamin in breast milk is somewhat academic. In a few studies made at the Boston Directory by Dr. Harold Teel, little effect could be shown to have resulted by rapid freezing on the small amount of ascorbic acid in pasteurized milk. Munsell[30] states that vitamin A is not altered by the temperatures of boiling and thus of pasteurization, and also that the content of this vitamin is not decreased by freezing and thawing. Some feeding experiments with human milk preserved by various methods led Eddy and Morris[31] to the conclusion that frozen human milk retained its vitamin A content better than that which had been preserved by evaporation to dryness. A few measurements made for us directly from preserved and freshly pasteurized specimens of human milk by Dr. J. F. McCreary in 1940 showed a loss of about one-third of the vitamin A to occur whether the milk was frozen very rapidly or comparatively slowly. The various components of the B complex which are present in human milk have not been studied with respect to the effects of temperature, although Rose[32] gives some evidence to suggest that whereas pasteurization might lower the thiamine and riboflavin values, freezing would probably bring about no further reduction. Although human milk does possess a certain antirachitic value, its vitamin D content is so low that no investigations of the effect of physical processes upon that substance seem warranted.

In general, there is reason to conclude that the necessary process of pasteurization lowers the amount of vitamin C in human milk just as in cow's milk but does not otherwise alter its nutritional value, while the useful preservation process of slow freezing may also diminish the content of vitamin A. Whether this is sufficiently depressed to require a vitamin A supplement (as well as one for vitamins C and D) might well be investigated.

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A COMPARISON OF GENTIAN VIOLET AND HEXYLRESORCINOL IN THE TREATMENT OF PINWORM INFESTATION

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DURING the past few years numerous investigations have proved the high incidence of pinworm infestation in various parts of the United States and Canada.[1-3] It is only natural that many types of therapy have been advocated for the eradication of this intestinal parasite.[4] Of the different forms of treatment proposed, two have apparently given outstanding success, hexylresorcinol (caprokol pills*)[5] and gentian violet.[6, 7] Considerable impetus to the use of gentian violet followed the introduction of an enteric coating (seal-ins†) which does not release the drug until four and one-half hours after being swallowed, thus avoiding most of the gastric irritation. Reports on the use of hexylresorcinol[4, 5] and other reports on the use of gentian violet[6, 7] indicate that these two drugs are effective in a fairly high percentage of cases in the eradication of *Enterobius (Oxyuris) vermicularis.*

In order to compare the effectiveness of these two drugs in the treatment of pinworm infestation, a group of children in an orphans' home was selected. The superintendent of the institution and each member of the staff were unusually cooperative; therefore we were able to make a much more careful and intensive survey than ordinarily would have been possible. Approximately 100 individuals were included in this study. They ranged in age from 6 months to 23 years, the majority being between the ages of 8 and 14 years. There was some change in the population under study during the time of the survey due to the fact that some children left the institution and new children were admitted. The children of school age attended public schools, and children of all ages were allowed to visit frequently in private homes. In spite of the fact that the group did not constitute an absolutely closed population, the use of a group of institutionalized children permitted relatively close supervision over the diagnostic tests, administration of therapy, and post-treatment check-up to ascertain the result of treatment.

METHOD OF STUDY

The children were examined by means of a modification of the NIH cellophane swab technique[8] as follows: Cellophane of the nonwater-

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*The Caprokol pills used in this investigation were kindly furnished by the Sharp & Dohme Co.

†The gentian violet Seal-Ins used in this investigation were kindly furnished by the Seal-Ins Laboratories, Inc.

proof type was cut into strips slightly smaller than the size of standard slides, and one of these strips was wrapped around the smooth end of a glass rod. After swabbing the perianal region, the cellophane strip was removed from the glass rod, placed on the slide with the clean surface of the cellophane uppermost, and then secured with a gummed label on which the name of the child was written. Each child was swabbed in this manner on seven consecutive mornings as soon as he got out of bed, before having a bath or a stool. No child was considered free of pinworm infestation until seven negative swabs were obtained. During the course of the survey, at least three stool specimens from each child were obtained and examined for ova.

RESULTS OF SURVEY

One hundred and two children were examined, and 80 (78 per cent) were found to be infested with *Enterobius vermicularis*. It is significant that routine stool examination revealed only four of this group to have this parasite.

Signs and Symptoms.—All the children were questioned as to various signs and symptoms which might be the result of pinworm infestation, and the matrons in charge of each group of children were questioned also to gather the same information. The signs and symptoms searched for were as follows: loss of weight, pallor, anorexia, pruritis, enuresis, vaginitis, nausea, vomiting, and restlessness. Ten of the girls did have vaginitis, which in every instance was relieved during the subsequent treatment for pinworm infestation. The other signs and symptoms occurred so infrequently or were so vague that it would be difficult to attribute them to pinworm infestation.

TREATMENT

The 80 infested children were divided into two equal groups comparable as to age and sex. One group was treated with hexylresorcinol (caprokol pills) in a dose of 12 mg. per pound of body weight, the maximum single dose being 1 Gm. This drug was given once a week for five consecutive weeks. It was administered in the morning and the patient was encouraged to drink two glasses of water. No breakfast was allowed, and nothing except water was permitted for the next five hours. This period of fasting is necessary to minimize vomiting. The other group was treated with gentian violet (seal-ins) having the four and one-half hour timed enteric coating. The dosage used was 1 mg. per pound of body weight per day, this dosage being divided into three approximately equal doses and administered thirty minutes before each of the three meals. This adjustment of the size of the three doses was simplified by the use of two sizes of gentian violet pills, one which contains $\frac{3}{20}$ gr. (10 mg.) and the other which contains $\frac{1}{2}$ gr. (32 mg.). The drug was given every day in this manner for one week; then a rest period of one week was allowed, followed by a

week of treatment, then another rest period of one week, and finally a third week of treatment. Thus the entire course of the treatment covered five weeks. No enema treatment was included in our regime, because we were primarily interested in comparing the efficacy of the two drugs when orally administered.

REACTIONS TO DRUGS

In one case treated with hexylresorcinol, the child chewed the pill and this resulted in a phenol-like burn of the buccal mucous membrane, which fortunately caused very little discomfort. In eight of the forty cases given hexylresorcinol, there were nausea and vomiting of considerable degree. The dosage was reduced in these eight, and four of these children were continued on the same drug with no further trouble. Because of persistent nausea even on the reduced dose of hexylresorcinol, the other four children were shifted to gentian violet treatment, which was well tolerated.

There were very few reactions in the group treated with gentian violet. Only one child out of the forty given this drug had nausea and vomiting. Two other children suffered only nausea. These three children were continued on gentian violet therapy in the same dosage and had no further nausea or vomiting. There were no other complaints attributable to the gentian violet medication. Therefore, only 7.5 per cent of the children treated with gentian violet were bothered by the drug, and in each case continuation of the drug in the same dosage caused no further reactions. The dose we used was 1 mg. per pound of body weight per day. This is different from the scheme advocated by Wright and Brady[6] and employed by other investigators; namely, $\frac{3}{20}$ gr. (10 mg.) for each year of apparent age. We have purposely given our group of children this reduced dosage (approximately 25 per cent less than is usually administered) because we desired to reduce the incidence of gastrointestinal irritation. That we succeeded in doing this is shown by the low incidence (7.5 per cent) of nausea and vomiting, most of which was of only slight degree, in contrast to the incidence of 23 per cent reported by Wright and Brady.

RESULTS OF TREATMENT

In order to determine the efficacy of this plan of treatment, a period of four weeks was allowed to elapse after the date of the last treatment. Then a second series of seven anal swabs was examined from the whole group, including treated and untreated children. This interval of four weeks was selected so that in any patient not completely freed of pinworms there would be time for the remaining pinworms to multiply and deposit ova at the anus. Of the original forty cases receiving each drug, some had moved away from the institution and were not available for re-examination. As shown in Table I, gentian violet medication was effective in curing 74.3 per cent of the children to whom it

was given, and hexylresorcinol was successful in 50 per cent of the children to whom it was administered. The arbitrary criterion of cure we adopted is that a patient have seven consecutive negative anal swabs.

The four children who suffered from nausea and vomiting when given the hexylresorcinol and who were given the routine dose of gentian violet are not included in Table I. All four were cured of *Enterobius* infestation. If these are included with the gentian violet-treated cases, we have thirty cures among the thirty-nine treated with this drug, or 77 per cent cures.

TABLE I

CHILDREN TREATED WITH HEXYLRESORCINOL		CHILDREN TREATED WITH GENTIAN VIOLET	
Number of Cases	34	Number of Cases	35
Number of Cases Negative on Post-Treatment Swabs	17	Number of Cases Negative on Post-Treatment Swabs	26
Percentage of Cures	50%	Percentage of Cures	74.3%

At this examination, four of the eighteen children who had previously shown seven consecutive negative swabs were positive. Also, nine new children who had been admitted to the institution during this interval were examined, and six of these nine showed pinworm ova. This is evidence that infestation is constantly taking place and that there is ample opportunity for the entire population of the institution to become reinfested, in spite of the large number of children whom the medication apparently cured.

DISCUSSION

This survey of an orphans' home confirms the findings of investigators in various parts of the country that infestation with *Enterobius vermicularis* is very common, that either hexylresorcinol or gentian violet may be used to eradicate the parasites from the intestinal tract, and that reinfestation occurs with ease. Such reinfestation can occur even in an institution where considerable attention is paid to cleanliness, as is the case in the home where this investigation was carried out.

We believe that gentian violet medication causes considerably less nausea and vomiting than hexylresorcinol and is easier to administer. It does not inconvenience the patient as does the five-hour fast imposed upon him after taking hexylresorcinol. The percentage of cures after giving gentian violet was 77 per cent; after hexylresorcinol it was 50 per cent.

The reduction in the dosage of gentian violet proved to be a sound policy, as reactions were infrequent and the percentage of cures was high. It may well be that the success of this regime of therapy is partly attributable to the extra week of treatment.

Because of the ease with which reinfestation takes place, it is not such a radical policy to treat every member of a household where any

one member is known to have enterobius infestation. Likewise, it may be necessary to repeat the treatment some weeks or months later. In institutions the only means of control of the infestation would be periodic repetition of the treatment.

Except for a few instances of vaginitis, the signs and symptoms usually attributed to pinworm infestation were not observed to a significant degree in this group of children.

CONCLUSIONS

1. Seventy-eight per cent of the individuals in an orphans' home were found to be infested with pinworms *(Enterobius vermicularis)*.

2. The value of the NIH cellophane swab method of diagnosis was clearly evident, and the failure to discover ova of this parasite by routine stool examination was demonstrated.

3. Patients seemed to tolerate gentian violet better than they did hexylresorcinol.

4. Smaller doses of the drugs were given over longer periods of time with considerably less reactions than previously reported.

5. Gentian violet was effective in 77 per cent of the cases; hexylresorcinol was effective in 50 per cent.

6. The ease with which reinfestation may occur was demonstrated.

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NEUROFIBROMATOSIS OF THE BLADDER IN A NINE-YEAR-OLD BOY

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ONLY ten cases of neurofibromatosis of the bladder have been reported in the literature. A 7-year-old boy described by Kass[6] is the only case reported occurring during childhood. Three cases in adults are in the American literature,[8, 9, 12] and six cases are in the foreign literature.[2, 4, 7, 10, 11]

The case reported in this paper is a child born in the Louisville City Hospital Dec. 19, 1931. He had very frequent upper respiratory infections from 7 months of age until 8 years of age and had had bilateral suppurative otitis media during four years of this time. He was admitted to Children's Free Hospital in 1934 and 1935 for idiopathic splenomegaly. All blood and urine findings were negative on these admissions.

In 1933 there was one week during which he had oliguria, edema of the feet and ankles, swelling of the abdomen, and jaundice. From 1935 to 1940 he had difficult respiration, and asthmatic râles in the chest clearing spontaneously.

He was admitted to Louisville City Hospital again in 1937 with the complaints of dysphagia, nasal speech, poor muscle tone, and suggestive paralysis of the soft palate. On physical examination he had a temperature of 101° C., a stiff neck, and a "paralyzed" bladder. A mass 1.5 cm. in diameter was found at the mucocutaneous junction of the anus. There was atrophy of the gluteal muscles on the right side, and x-rays of the sacrum showed incomplete sacralization.

He was readmitted to the Children's Free Hospital in 1939 with the same findings as above. A psychometric examination at this time showed normal intelligence.

The mother of the child has multiple neurofibromas of the skin (Fig. 1) and multiple pigmented areas on the surface of the body but a negative fluoroscopic examination of the skeleton. The patient is the sixth of nine children. The first, sixth, eighth, and ninth children have multiple areas of pigmentation on the skin but no evidence of tumors in the skin. No other history of von Recklinghausen's disease in the family is found.

The patient was readmitted to the Louisville City Hospital Aug. 15, 1941, for a checkup. He was 9 years old and weighed 39 pounds. He had been getting along very well. There were no urinary symptoms and his only complaint was occasional mild pains in his legs.

On physical examination there were multiple, various sized, brown, pigmented areas scattered over the entire surface of the body. These were not elevated and had no hairy growth in them and were not thicker than normal skin. He had a marked dolichocephalic head which was held slightly to the left. There was a deviation of the uvula to the left, but a good gag reflex was present. The heart and lungs were normal. The liver and spleen were not palpable. The bladder was two fingers above the symphysis, hard, and movable. On rectal examination, the bladder was the size of a large orange and felt like an immense prostate. The ligaments to

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each side of the bladder were thickened. There was no tenderness. There was a mass 1.5 cm. in diameter at the mucocutaneous junction of the anus which felt like a lipoma. There was a marked atrophy of the gluteal muscles, a heavy thick skin with an abundance of hair over this region, and a pad of fat over the sacrum. There was some loss of sensitivity of the skin over the left anal region (Fig. 1). Reflexes were physiologic and active.

Fig. 1.

The department of neurology felt that they had nothing to offer this patient. He was cystoscoped by the urological department, and the impression of tumor of the prostate or retroperitoneal sarcoma was obtained.

Repeated urinalyses were negative. There was no residual urine. The nonprotein-nitrogen, Mosenthal, and phenolsulfonephthalein tests were negative. There was 2.0 Gm. of urinary P_2O_5 in a twenty-four-hour specimen and 0.46 Gm. of urinary CaO in a twenty-four-hour specimen. There were 3.8 mg. and 5.6 mg. of inorganic blood phosphorus per 100 c.c. of serum on two specimens. There were 15 mg. of blood calcium per 100 c.c. of serum.

Intravenous pyelograms showed a double kidney and ureter on the left side and an essentially normal cystogram (Fig. 2). X-rays of the long bones gave an estimated bone age of 7 years. X-rays of the sacrum showed a wide-open sacral canal indicating spina bifida. There were no cystic areas in the bones.

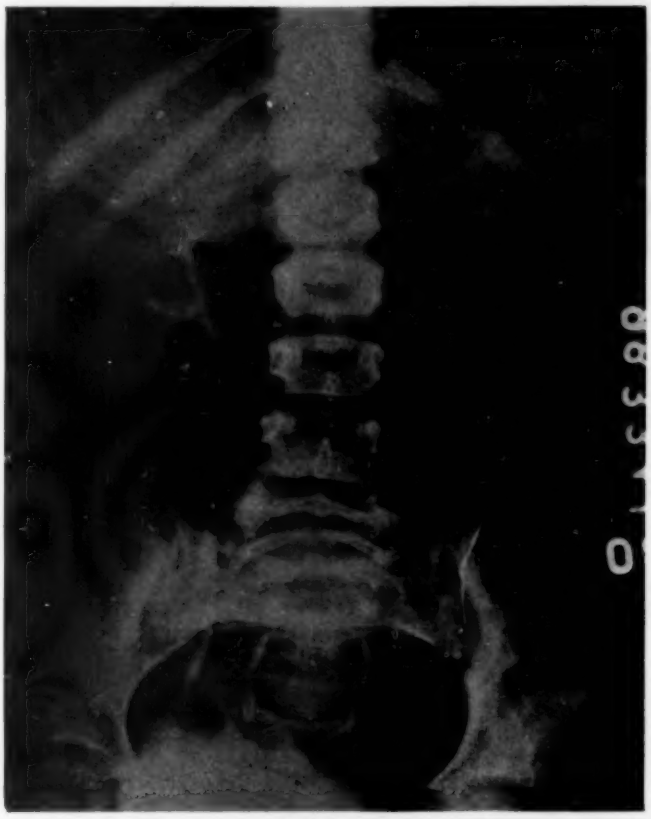

Fig. 2.

On Sept. 16, 1941, an exploratory laparotomy was done and the entire bladder was found to be thickened. Posteriorly it was approximately 4 cm. in diameter, and anteriorly 1½ cm. in diameter. It had the appearance of tapioca shining through the peritoneum, and the infiltration extended up the ureter 2 cm. on the right and 3 cm. on the left. The mucous membrane of the bladder was normal.

A biopsy was done and frozen sections were made which revealed no definite neoplasm, so that the patient was closed without further operation. The child made a normal postoperative recovery and is doing well two months later.

Histopathology.—Sections of the bladder musculature revealed multiple islands of tumor tissue, well circumscribed, scattered diffusely throughout the sections, lying between and among the muscle fibers (Fig. 3). These islands are, for the most part, round and vary in size from microscopic to 1 to 2 mm. millimeters in diameter. The cells composing them are spindle shaped with ovoid nuclei, and their cytoplasm

seems to have long fibrous processes. The cells are not tightly packed, and the delicate matrix is pale pink or pale blue, giving the picture of a delicate young connective tissue. There are no mitotic figures, invasiveness, or other evidences of malignancy (Fig. 4).

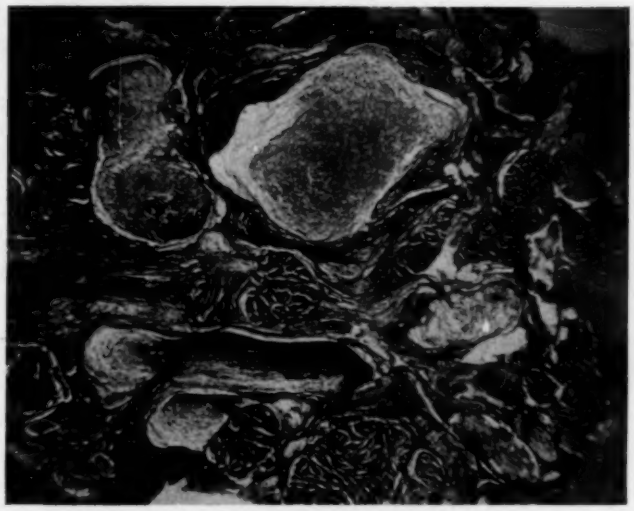

Fig. 3.

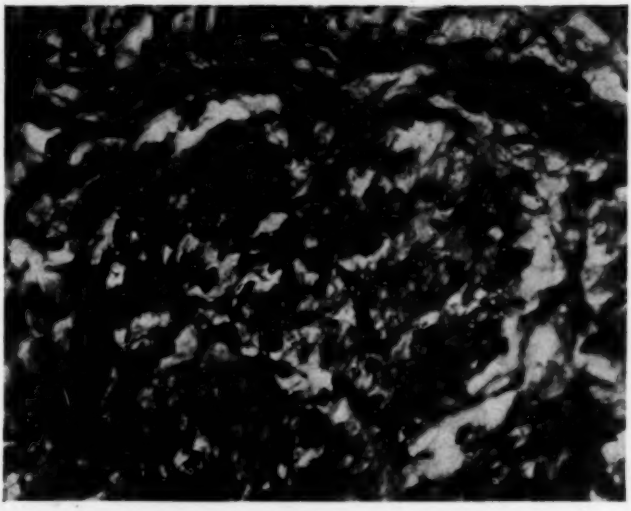

Fig. 4.

DISCUSSION

The case presented in this paper is undoubtedly von Recklinghausen's disease. The patient was brought to surgery because of an undiagnosed

tumor of the pelvis. Because of its rarity, no one suspected neurofibromatosis of the bladder.

Although a biopsy was necessary for the diagnosis and handling of this case, it has been shown by Harbitz[2] and Hosoi[5] that operative procedures may cause sarcomatous changes. It has been decided to treat this boy expectantly, primarily by transplantation of the ureters in the event of any obstruction to the urinary tract.

The nutrition will be difficult to maintain as he is already 25 pounds underweight and has not gained under hospital supervision.

SUMMARY

The second case in the literature of neurofibromatosis of the bladder occurring during childhood is presented. There is a history of von Recklinghausen's disease in the family. The case is complicated by congenital malformations.

We wish to express our appreciation for the cooperation of Dr. A. J. Miller for the photographs and pathologic interpretations.

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Round Table Discussion on Hemorrhage in the Newborn Infant

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Introduction

Stewart H. Clifford, M.D., Boston

The susceptibility of the newborn infant to abnormal bleeding is one of the major hazards of this age period. The effect of this hemorrhage is only partly due to the actual blood loss; the greatest injury is that secondary to the extravasation of blood in vital tissues. The purpose of this round table is to discuss the diagnosis, prevention, and treatment of hemorrhage in the newborn infant.

However, before we can approach our objective we must establish a common ground upon which we can all agree and from which our discussion can depart. The literature fully recognizes the confusion that surrounds the subject of "Hemorrhagic Disease of the Newborn Infant." All agree that much of this confusion arises from the lack of a definition of this condition to which all authors will subscribe. The plan of this round table is to clarify the situation rather than to add to the confusion, and to do this we as a group must eventually be able to agree among ourselves on the definition as to what, if anything, shall be defined as hemorrhagic disease.

The Physiology of the Blood in the Newborn Infant

H. G. Poncher, M.D., Chicago

During the last decade much progress has been made in the field of the chemistry of blood coagulation, but there are at least seven outstanding theories which have been advanced to explain the clotting of blood. While no two theories completely agree as to the exact mechanism in blood coagulation, a certain unanimity of opinions exists among various investigators as to the essential factors concerned in clot formation. Using the most widely accepted terminology, the essential factors are

(1) prothrombin, (2) thromboplastin or thrombokinase, (3) calcium, and (4) fibrinogen.

With the exceptions of the hypotheses proposed by Mellanby in 1934 and Nolf in 1938, practically all theories concede that plasma prothrombin is first activated by thromboplastic substance or substances in the presence of ionic calcium to form an active enzyme (thrombin) which in turn converts fibrinogen to fibrin. The dissimilarities of the various theories originate chiefly in the inherent nature of the reactions and by reason of where the major emphasis is placed in the physiologic roles played by a variety of clot-promoting and clot-preventing substances in the plasma.

In its simplest form the classic conception of blood coagulation recognizes two stages of reactions which may be briefly outlined as follows:

(1) The conversion phase
Prothrombin + thromboplastin + Ca (thrombokinase) – thrombin
(2) The coagulation phase
Thrombin + fibrinogen – fibrin

Heparin and other physiologic anticoagulants have been purposely omitted from the discussion in order to simplify the presentation. This information will be entirely adequate for the intelligent understanding and practical consideration of our subject.

Before applying these facts to the physiology of the clotting mechanism during the newborn period, let us briefly review the historic development of the subject. The existence of a bleeding tendency during the first week of life, independent of intercurrent disease, has been recognized in medical literature for over 200 years. In fact, some writers would dignify this observation by citing implications of this knowledge in the Mosaic law which states that ritual circumcision should be delayed until the eighth day after birth. Rodda, however, was the first to study systematically the coagulation time of the blood of the newborn infant and to point out that there was a physiologic prolongation of the clotting time which corresponded to the time of greatest incidence of hemorrhagic disease of the newborn infant.

While a prolonged clotting time indicates that coagulation mechanism is faulty, it gives no clue to the clotting factor at fault. Accordingly, a number of investigators in the past have attempted to elucidate the cause of spontaneous bleeding in the newborn infant. Lucas, Sanford, Maurizio, and Salmonsen found, as had Rodda, that the coagulation time was prolonged up to the third or fourth day and then returned ot normal by the end of the first week. Attempts to explain the cause of this prolongation were not successful since essentially normal values were found for platelets, fibrinogen, calcium, and bleeding time. Whipple had suggested a prothrombin deficiency as the basis for bleeding in the newborn, but his results were vitiated because they were performed on post-mortem blood. This observation was later confirmed, however, by the Iowa group who established by accurate chemical means that normal newborn infants showed low prothrombin values. Later this was confirmed by Quick and other investigators using more simplified methods. Since the drop in prothrombin time corresponded to the prolonged clotting time and the incidence of bleeding in the newborn, Waddell and his associates attempted to prevent the drop with vitamin K, which Dam had shown to be essential in the synthesis of prothrombin. The success which followed marks the beginning of an interesting chapter in the treatment of hemorrhage. However, even scientific glamour engenders prostitution, and vitamin K was used indiscriminately for all types of hemorrhage occurring in the newborn period.

When bleeding is encountered in the newborn, it is necessary to assess carefully the vascular and hematologic factors which might produce it in order to establish

a correct diagnosis and apply appropriate treatment. The first line of defense against hemorrhage is an intact vascular system and in the presence of injury or trauma the contraction of the capillary vessels is the first effort at hemostasis. During this period of capillary contraction, the intravascular clotting mechanism comes into play, and, if it is normal, a firm clot is formed. When the wounded vessels dilate, the clot prevents further bleeding. If the power to form an effective clot is lowered, bleeding may occur with minor vascular alteration, and conversely, if the vascular alteration is extensive, bleeding will occur in the presence of a normal clotting mechanism. It is therefore obvious that a patient may bleed in consequence of a disturbance in the vessel wall, in the intravascular clotting mechanism, or in both. Clinical examples of these various mechanisms will be discussed by the various members of this group.

The means by which the various types of bleeding may be accurately assessed is a matter of combined clinical and laboratory study. Information concerning the factor of vascular alteration must be obtained for the most part from history, for capillary resistance tests as ordinarily performed have yielded little reliable information. Bayer's statement that capillary resistance is decreased in the normal newborn infant is not verified by other investigators, yet it is well known that the factors which alter capillary permeability, such as stasis, trauma, infection, and anoxia, are constantly present during this period of life and are important factors in initiating bleeding or conditioning its severity. The vascular factor may also be indirectly assessed by a study of the clotting mechanism. The traditional clinical methods for determining the ability of the newborn infants' blood to clot are, however, open to certain objections. Nygaard has emphasized that clotting is a potential property and not a vital property of the blood. Accordingly, it would seem logical to use such tests which reveal this potential property. The first approach would be to determine the individual clotting factors, but this is too detailed for routine clinical work. The clotting time, therefore, came into vogue as a test which should express the summation of these factors and may be classed as a "screening test" in hemorrhage. However, it should be borne in mind that when blood is drawn and tested for its clotting ability, factors are introduced which are not present in spontaneous hemorrhage and the results should therefore be evaluated in the light of the technique employed. A coagulation time of fifteen minutes, using venous blood, may be just as normal as three minutes where capillary blood is used. Wet glass, presence of air in the syringe, changes in temperature, depth of the prick, presence of tissue juice, and amount of surface over which the blood is spread all tend to alter the coagulation time.

Since the objectionable factors of the capillary blood methods all tend to shorten the time and since it is the method which is most commonly used in the newborn period by practitioners, one may regard the objectionable features of the method to be only of academic interest. Practically, one may safely assume that a clotting time of eight to ten minutes or over constitutes a significantly prolonged value. Conversely, however, a coagulation time below eight minutes by the capillary method is no assurance that the clotting mechanism is normal. The various clotting elements are enormously in excess of what is needed for coagulation so that a significant diminution of one element may be associated with a coagulation time which falls within normal limits. Besides, the thromboplastic substances from the wound would further tend to shorten the coagulation time. The next question arises as to what factor in the clotting mechanism is at fault, prothrombin, calcium, thromboplastin, or fibrinogen. For practical purposes the determination of the prothrombin time is the most expedient test for determining the cause of bleeding in the newborn period. Since methods are now available which can be used at the bedside, the test can be employed in everyday practice. Aside from alteration in the vessel wall, hypoprothrombinemia is the most common cause of spontaneous bleeding in the

newborn period. Hemophilia rarely manifests itself in this period unless through extensive trauma or surgical intervention, and cases of congenital thrombocytopenia and fibrinogenopenia are rare. Bleeding on the basis of calcium deficiency is theoretically possible but practically nonexistent. I have yet to see a case of tetany of the newborn where bleeding was etiologically connected with the hypocalcemia, and no reports of this type have come to my attention.

From these clinical rationalizations it would appear that the most practical test for information as to the defective clotting mechanism in the newborn period is prothrombin time estimations. A number of such methods are available, but the various microadaptations of the Quick technique are the most practical for clinical work in the newborn. A prothrombin time of 20 per cent of the normal adult value, or below, is significant in spontaneous bleeding, but values from 20 to 40 per cent may play an important role in conditioning bleeding in the presence of vascular damage. In a curve constructed by Quick, the plasma may contain 50 per cent of normal prothrombin and yet the prothrombin time may vary only about four seconds. The blood normally contains several times the amount of prothrombin necessary to produce coagulation within normal limits.

Though there is no absolute relationship between the prothrombin level and the appearance of spontaneous hemorrhage, a value of 20 per cent of the normal adult value, or below, is usually critical. Smith and his co-workers at Iowa report that the whole blood clotting time becomes prolonged in chicks on a vitamin K-deficient diet when the prothrombin level reaches 30 per cent of normal and hemorrhages make their appearance at the level of 10 per cent. The following observations of Edsall are generally in keeping with clinical experience:

Infants with titers of 15 to 30 per cent do not always bleed, but when they do the hemorrhage is severe; whereas infants who have titers above 30 per cent, though they might bleed, do not manifest more than a transitory hemorrhage. Those below 15 per cent bleed severely.

These statements may be correlated with the facts presented in Clifford's critical review of "Hemorrhagic Disease of the Newborn" published some years ago. He found a significant difference between infants with external and internal bleeding. Other observers have found that cases with melena or hematemesis alone usually present less severe bleeding than other types of hemorrhage, although one cannot be dogmatic on this point. A probable explanation may be that those sites of external bleeding are predisposed to hemorrhage not solely by absolute level of prothrombin but by some factor altering the integrity of the vascular system as well. The alimentary tract is apparently such a site, as occult intestinal blood is quite frequent in the normal newborn infant. Accordingly, bleeding may take place even when the prothrombin deficiency is not so marked. Since the escape of blood is by diapedesis, spontaneous arrest of the hemorrhage may be possible. Salmonsen, Grab, Bayer, Berheim, Karrer, and other observers found that infants with melena have a normal coagulation time or only slightly prolonged. Of the fifteen infants in Salmonsen's sixty-two cases of hemorrhagic disease who did not have a prolonged coagulation time, nine were infants with melena. In our experience infants with so-called hemorrhagic disease with the least prolongation of the prothrombin time have also been those with melena. This point is not sufficiently absolute, however, to justify a statement that melena is always associated with higher levels. We cannot concur with the statement of Salmonsen that the coagulation time is invariably prolonged in hemorrhagic disease of the newborn and that "the reason this has not been unanimously observed is due to the fact that investigations, to a large extent, have been limited to cases with melena." In his series of sixty-two cases, forty-seven were observed to have significantly prolonged coagulation times. However, he did not find a uniform correlation between coagulation time and the number and intensity of hemorrhages. While a definitely prolonged prothrombin

time is usually associated with spontaneous bleeding, this is not invariably the case. The same phenomenon is seen with prolonged coagulation times in hemophilia and in patients with marked thrombocytopenia in Werlhof's disease. MacFarlane recently reported a case of a child who had a congenital lack of fibrinogen which rendered his blood incoagulable and yet he reached the age of 8 years without clinically important hemorrhage. These observations stress the reciprocal relationship that exists between vascular factors and the intravascular clotting mechanism.

Hemorrhagic disease of the newborn is constantly associated with a prolonged prothrombin time and this is quickly restored to normal by vitamin K. The exact mechanism by which this condition is brought about is at present unknown. Speculations center about an inadequate storage of vitamin K during fetal life which is inadequate to sustain the infant the first few days after the maternal supply is cut off and while the infant is developing an endogenous supply from his bacterial flora in the intestine; or about a functional insufficiency of the liver whereby that which is present is not efficiently utilized, or both. The maternal supply factor is difficult to evaluate as I have yet to find a mother giving birth to an infant with hemorrhagic disease of the newborn who had evidence of prothrombin deficiency. Other workers have also found that the prothrombin value in the mother was greater than that of her infant, and the correlation between the prothrombin time of the infant and of the mother is low. There also appears to be no correlation between the dietary intake of the mother and the prothrombin level of the newborn (Kove and Siegel). Maternal prothrombin deficiencies on a dietary basis are difficult to evaluate, for it has been shown that a patient who has been on a vitamin K-free diet for five days will pass stools, the ether extract of which may contain as high as 2,000 Dam units of vitamin K per gram. Why the maternal endogenous sources do not become more available to the fetus while vitamin K in the form of concentrates or synthetic preparation does is difficult to explain. Tocantins offers the explanation of a functional insufficiency of the liver. Norris and Bennett believe it unlikely that prothrombin passes directly from mother to fetus, and they think it possible that prothrombin may be formed by the placenta since blood coming from the placenta has a higher prothrombin value than that entering it from the baby. This still does not explain why normally the prothrombin time increases twenty-four hours after birth but remains normal if the mother is given vitamin K concentrates or synthetic form prophylactically before delivery (Waddell and Querry, Shettles, Delfs and Hellman, and others). Quick and Grossman ascribe the low prothrombin values they encountered on the second and third days to inadequate fetal storage. Grossman suggested additional factors such as decreased absorptive ability of fat-soluble substances, inadequate bile secretion, and intestinal hypermotility.

In the normal newborn infant a spontaneous rise in the level of prothrombin occurs by the fifth day. The source of vitamin K which brings about this restoration has been suggested by Quick to be that which is synthesized by bacterial action in the intestine. Working on this observation some investigators have advised that the newborn be supplied with milk earlier than usual to encourage the endogenous synthesis of vitamin K, and results are reported by some to substantiate this suggestion (Salmonsen and Nygaard). The recent report by Gellis and Lyon would seem to corroborate this observation.

While it is probably true that bacterial synthesis in the intestine is an important source of endogenous vitamin K, it is difficult to imagine why such sources would not become available to infants with hemorrhagic disease since no defect in intestinal absorption or liver pathology has been demonstrated.

Almquist has shown that in comparative potencies of the hemorrhagic activities of certain microorganisms (using alfalfa as a standard of 1), *Bacillus cereus,*

B. mycoides, and *B. subtilis* have values of 23, 31, and 38, respectively. These bacteria are all air-borne spore-forming aerobes and would infect the mouth and gastrointestinal tract whether food is offered or not. In comparison to these bacteria, Almquist reports a comparative value of 3 for *B. coli*. Molds, yeast, and fungi were uniformly inactive. Such facts, interesting as they are, carry us far afield of the purpose of our discussion. We can summarize this controversial phase of the subject by stating that bacterial synthesis is an important endogenous source of vitamin K for the human organism and is probably more important than the most potent of the exogenous dietary sources, the green leafy plants. It is also of interest that the vitamin appears to be the richest in the photosynthetically active parts of the plant since, as Almquist has shown, carrot tops are a good source while carrot roots contain no detectable quantity.

In the management and prevention of hypoprothrombinemic states (other than those due to liver damage) during the newborn period, our main interest is concerned with vitamin K concentrates or the pure synthetic forms and their esters. The progress made in the isolation and purification of natural forms of vitamin K and synthesis of their analogues is phenomenal and deserves more than the brief consideration which they will receive in this discussion. Since vitamin K_1 was isolated from alfalfa, other naphthoquinones and their analogues have been synthesized and made available for clinical use. Many of them possess to a greater or less extent the activity of natural vitamin K. It does not follow, however, that all of the analogues of this vitamin are of comparable potency, and biologic standardization is necessary. At present the subject is a bit confused by the fact that unitage is expressed on the basis of different methods of assay, using variable lengths of time for a curative test period. As an example, 1 Anspacher unit is equivalent to 20 Dam units, while 1 Thayer-Doisy unit is equivalent to 30 Dam units. Almquist and Stokstad find 1,000 units for the 1 mg. of the 2-methyl-1,4 naphthoquinone form by their method of assay. While there is no commonly accepted biologic unitage, and until such data are forthcoming, it would seem desirable to express the potencies of various compounds in comparison to compounds of known clinical and laboratory potency such as 2-methyl-1, 4-naphthoquinone (K_3).

Vitamin K_1, or 2-methyl-1, 4-naphthoquinone, is a fat-soluble vitamin and is given mainly by the oral route without bile salts unless there is biliary or intestinal obstruction. It is available commercially under a variety of trade names* which often confuse the practitioner. It may be dissolved in corn oil (menaquin) and other vehicles and be given intramuscularly. When combined with sodium bisulfite (hykinone) or sodium disulfate and other chemicals, it is rendered water soluble and stable and can be given intravenously in addition to the other routes. Olwin reported that the crystalline form of 2-methyl-1, 4-naphthoquinone (menadione) can be given intravenously in a 0.01 per cent solution in distilled water after suitable preparation and preservation. Russell and Page have recently reported successful prophylaxis of newborn infants with the percutaneous use of 2-methyl-1, 4-naphthoquinone in a special ointment base of 1 per cent strength. One application of 10 mg. is rubbed thoroughly on the back on the first or second day after birth. None of the twenty-four infants treated in this manner showed hypoprothrombinemia, while a similar number of control infants showed the usual physiologic hypoprothrombinemia. The 4-amino-2 methyl-naphthol hydrochloride, K_4 (synkamin), successfully synthesized by Doisy and his group, is wafer soluble and compares favorably with the K_1. This may be given parenterally by any route and by mouth. Other analogues of vitamin K are available commercially, but the ones previously mentioned have had the most extensive clinical trial and will form the basis for this discussion.

*Proklot, Thyloquinone, Kayquinone, Menadione.

It is difficult to get very sanguine about slight differences in rscommended dosages, as the range of therapeutic safety is large and it would seem feasible to err on the side of safety. It has been suggested that large doses may effect recovery more rapidly than small doses, and that if the body has a decreased ability to form prothrombin, large doses may permit more effective use of whatever capacity remains for prothrombin synthesis. From our experience gained in the therapy of prothrombin deficiency states of extrahepatic origin in the newborn, one would be safe in recommending as necessary only 1 to 2 mg. of the water-soluble preparations, or their molecular equivalents, parenterally, as late as from six to four hours before delivery and 5 mg. of the fat-soluble preparations from ten to six hours before delivery, where bile secretion is normal and no defect of intestinal absorption exists.

Since the toxic symptoms can be produced only by excessive doses and there is no danger of producing a hyperprothrombinemic state or thrombosis, vitamin K has been routinely given to pregnant women and newborn infants. Dr. Waddell will discuss the results and validity of this practice. So far as the effect on the prothrombin time is concerned, it can be definitely stated that if oral preparations are given to a normal pregnant woman twenty-four to twelve hours before she goes into labor, or if vitamin K is administered daily before delivery the prothrombin time of the infant will be normal and there will be no untoward effect on the mother. Water-soluble preparations given parenterally will be effective in prophylaxis when given as late as one hour before delivery, although it is desirable to have a longer interval to obtain the maximum effect. The dosage recommended is 2 mg. daily of the oral preparations and a single dose of 2 mg. of the water-soluble parenteral preparations at least from six to four hours before delivery. There would seem to be little advantage in giving oral prophylactic therapy more than a week before labor as there is no evidence for a cumulative effect. In fact, a single oral dose of 5 mg. at the start of the first labor pain may be practical in most cases. If a woman goes into labor without adequate prophylaxis, a single dose of a parenteral preparation can usually be given in a sufficient time to be effective before she delivers. The same dosage can be given prophylactically to the infant at birth but need not be repeated unless the infant is premature. In such infants we have found that the physiologic hypoprothrombinemia is not infrequently present after the first week. For therapeutic purposes, I prefer the parenteral preparations in doses of 2 mg. and repeated in twelve-hour intervals until the prothrombin value returns to normal or bleeding has stopped. In our earlier work I never used more than a single 1 mg. dose intramuscularly of water-soluble K_s (synkamin) in the most severe case of hemorrhagic disease and obtained excellent therapeutic results. It is possible, however, that there are cases which require larger doses. If such be the case, liver pathology should be ruled out. It would seem logical especially to practice prophylaxis in all prematurely born infants, those born of toxemic mothers and those subjected to severe trauma and asphyxia at birth, as these patients are particularly liable to hemorrhage and it is desirable to have all clotting factors present in normal concentration. In our experience and in the experience of others, premature infants are apt to have longer prothrombin times than full-term infants. Similarly, infants subjected to surgical intervention during the first week of life and those having had hemorrhage from any cause should be given vitamin K to replenish prothrombin which has been utilized in the arrest of hemorrhage.

In summarizing, I think one can categorically state that vitamin K and its analogues are effective in prevention and treatment of all hypoprothrombinemic states encountered in the newborn period which are not due to extensive liver damage; that restoration of prothrombin levels to normal invariably follows administration of adequate doses of vitamin K (if it is given by routes which will facilitate absorption), and cessation of bleeding follows if deficiency of prothrombin is the causative factor in the hemorrhage.

It is also clear that vitamin K therapy will not influence the incidence of hemorrhage on a vascular basis (unless prothrombin deficiency exists) or those conditions due to a deficiency of clotting factors other than prothrombin. Practically all newborn infants exhibit hypoprothrombinemia in various degrees during the first week of life, but, unless the value drops to about 20 per cent of normal or below, spontaneous hemorrhage is rare. Milder degrees of hypoprothrombinemia may influence the duration and extent of the bleeding on a vascular basis (if damage is not too extensive) without influencing the incidence, for one would not expect vitamin K to prevent the onset of hemorrhage of vascular origin. The clinical indications are thus clearly drawn, and the ensuing discussion will challenge or verify the validity of these statements.

Hemorrhage in the Newborn of Septic and Traumatic Origin and From an Improperly Tied Cord

Dr. C. E. Snelling, Toronto

One general fact has been established in the discussion of the physiology of the normal newborn blood, and that is that in the newborn period blood has a lower prothrombin and as a result of this there is a greater tendency to hemorrhage. This must always be borne in mind when considering hemorrhages in this period which are secondary to other causes, such as sepsis, syphilis, and trauma, because hemorrhage once initiated is more prone to continue with low prothrombin in the blood. Secondary bleeding during this period may result from a number of causes. Many of these will be illustrated.

HEMORRHAGE FROM AN IMPROPERLY TIED CORD

A 7-pound male infant* was normally delivered at full term and was known to have been inspected at the age of 2 hours when his temperature was recorded and no unusual findings were noted. At the age of four hours the infant was found in a pool of blood, estimated at approximately 200 c.c., exhibiting obvious signs of exsanguination.

Repeated attempts to transfuse the baby failed because of peripheral collapse of the blood vessels. A large hypodermoclysis was given, but the baby died at the age of 6½ hours.

Inspection at the time of death showed that the two original umbilical ligatures had loosened markedly and that the additional two ligatures that had been applied had loosened similarly.

An autopsy confirmed the impression that the cause of death was acute hemorrhage. Two of the knots were square while the other two were false "grannies."

The cause of this condition is due to the cord not being tied securely or the ligature loosening or slipping, or, as is seen particularly in premature babies, the ligature cuts through a very friable umbilical stump. The pathologic and clinical changes are those of hemorrhage and exsanguination. The laboratory findings are those of lowered hemoglobin and red blood count. In the true accidental hemorrhage from the cord the bleeding and clotting times are normal and the prothrombin content is not unusual. However, umbilical bleeding may be associated with abnormally lowered prothrombin content; this will be discussed later by Dr. Waddell. Treatment is to stop the bleeding by applying a ligature which is effective, and if the child has lost sufficient blood a transfusion is indicated. The course and prognosis depend on how soon the condition is discovered and treatment instituted. The condition is eliminated by securely ligating the cord. This is an obstetric problem and in discussing it with members of the obstetrical departments at the Toronto General and

*I am indebted to Dr. Clifford for this case history from the records of the Boston Lying-In Hospital (Case history No. 29714).

Toronto Western Hospitals they state that it has been eliminated by the use of the Zeigler clamp on the cord. A simple method of cord ligature described by Kanner consists of a rubber elastic band pulled around the cord by means of a linen cord and this is fastened with a lead shot which has been compressed. By this method in a large series of cases he has had no failures and it has the advantage over the Zeigler clamp of being cheap, readily available, and not requiring a special instrument for removal, and it does not apply strain from the weight on the cord. It has been our personal experience to see two cases of bleeding from this source and both followed the usual hand-tied ligature.

SEPTIC CAUSES OF HEMORRHAGE IN THIS PERIOD

Syphilis.—Baby M. C. was admitted at 11 days of age with a complaint of bleeding from the umbilicus commencing one hour before admission. The child weighed 5 pounds at birth; birth history not given. On admission the infant was bleeding from the umbilicus but did not appear exsanguinated. The liver was palpable; the spleen was reported not enlarged. The red blood count was 3,700,000; hemoglobin, 70 per cent. The bleeding time was nine minutes and the clotting time, eleven minutes. Blood culture was negative. Blood Wassermann was four plus. The baby was given one transfusion and the bleeding stopped. Later he developed a nasopharyngitis, otitis media, and an acute nutritional disturbance and died. The mother had syphilis and had received no treatment prior to the birth of the baby.

At post-mortem there was found a small subtentorial hemorrhage. The liver showed increased fibrosis, particularly in the periportal zones. There was infiltration with lymphocytes and eosinophiles. The pancreas also showed an increased fibrosis.

According to Holt and McIntosh, bleeding at various sites is not uncommon in congenital syphilis during the newborn period, and as they state, "Delayed and prolonged bleeding from the umbilicus must always arouse a suspicion of syphilis." Older texts stated that bleeding occurring after the twelfth day suggested syphilis or sepsis. Grulee and Sandford state that hemorrhage in syphilis in the newborn often simulates erythroblastosis in the pathologic changes and hemorrhagic disease clinically. They state that the bleeding and clotting times may both be prolonged but that the clotting time is more likely to be. I have had no opportunity of measuring the prothrombin times in a case of bleeding as a result of congenital syphilis. It is quite possible that the prothrombin of the blood is reduced by the effect of the spirochete on the liver and that this is the factor in the production of the bleeding. Dr. Poncher and Dr. Waddell have both sent personal communications stating that the prothrombin is low in this condition.

In the case report sent by Dr. Waddell the condition was relieved by one administration of vitamin K intramuscularly. Dr. Poncher stated that the hypothrombinemia was restored by vitamin K, but the effect lasted only a short time and he felt that with widespread hepatitis the prothrombin level was not maintained after vitamin K administration.

The pathologic changes seen are those of congenital syphilis, and time does not permit me to elaborate further.

The clinical findings are hemorrhage starting after 10 days of age and other evidences of syphilis, such as snuffles, rash, prematurity, positive Wassermann reaction in the mother, and x-ray changes in the bones. The treatment is to transfuse in order to stop the hemorrhage and then institute antisyphilitic treatment. Regarding the hemorrhages, unless they are in a vital organ, the prognosis is good. The hemorrhages are usually fairly easily controlled. The prophylaxis is early recognition of syphilis in the mother with introduction of antisyphilitic treatment early enough that the baby will not be affected.

Sepsis.—Baby J. was admitted at 4 days of age with a temperature of 104.2° F., with a complaint of jaundice for one day, fever for ten hours, twitching for six hours, and bulging fontanel for six hours. He was a 7½-month term infant weighing 4 pounds, 7 ounces at birth and was born normally without instruments after a twenty-four-hour labor. The second stage was precipitious. The baby cried spontaneously and was a good color. The course was uneventful until ten hours before admission when the temperature rose. Later the baby began to twitch and the fontanel, which previously was not bulging, was observed to be fuller than normal and quite tense. On admission the baby was acutely ill, one pound under its birth weight, had a purulent discharge from the umbilicus, some stiffness of the neck, bulging fontanel, and was cyanosed. Bleeding and clotting times were normal. The urine passed in the diaper was blood-tinged. The baby died shortly after admission. At post-mortem examination the child showed a diffuse subarachnoid hemorrhage over the entire brain, the source of which could not be ascertained. In addition there were a few small hemorrhages between the leaves of the tentorium and falx. Blood culture and swab of the subarachnoid hemorrhage gave a pure culture of hemolytic streptococcus. Swab of the umbilicus revealed a mixed infection. Nothing else of particular note was found on post-mortem examination.

Sepsis in the newborn may gain entry from various sites; however, the umbilicus and skin seem to be most common, followed by the respiratory and gastrointestinal tracts. According to Dunham, bleeding was present in about 25 per cent of her cases. The commonly found organisms are streptococci, staphylococci, *B. coli*, pneumococcus, and *B. pyocyaneous*. Hemorrhages may occur from the umbilicus, the gastrointestinal tract, skin, or any of the mucous surfaces and may be the cause of death (Holt and McIntosh).

In sepsis of the newborn, inflammatory change may be found in almost any organ of the body. Bednar, in eighty-seven autopsies (Holt and McIntosh), found eight with meningeal hemorrhage.

The usual time for the temperature to rise is the third or fourth day, and following the temperature rise the symptoms will vary according to the organs affected. The normal picture is that of an acutely ill child frequently having gastrointestinal disturbance, twitching, and fretful sleeping. Blood culture reveals an infecting organism.

The use of chemotherapy has improved the outlook in the treatment of sepsis in the newborn. The course and prognosis of the hemorrhage and of the child as a whole depend largely on the early institution of treatment. This condition can be prevented by better care of the umbilicus and by avoiding infection in the newborn infant.

TRAUMATIC CAUSES

Cephalhematoma.—Baby G. was born after a normal labor of a primiparous mother. The first stage of labor lasted eighteen hours and the second stage, two hours. The position of the head at the commencement was R.O.P. Rotation occurred without difficulty and the baby was born normally, weighing 7½ lbs., following a small episiotomy. No difficulty was experienced in resuscitation; the baby cried and breathed well. A caput was observed at birth over the occiput. The following day the right side of the head posteriorly was noted to have a soft fluctuant swelling. This increased in size for two or three days and was limited in outline by the margins of the right parietal bone. It began to decrease in size after one week and at that time there was a sharp margin around the periphery. When seen at 6 weeks of age, the bony margin had spread over two-thirds of the swelling with a small soft area in the center. At 3 months of age the whole mass was ossified, smaller than previously but certainly still a noticeable swelling over the right parietal region. By 1 year of age the swelling had disappeared. At no time were

there any symptoms suggestive of increased intracranial pressure. Cephalhematoma is a hemorrhage between the periosteum and bone in the baby's skull. The usual type is exernal, but internal types have been reported. The latter are nearly always a result of fracture of the bone. The usual cause is a slipping of the periosteum on the underlying bone from the forward and back or rotating motion of the head which occurs in the passage through the birth canal. This causes a loosening of the periosteum much like the loosening that takes place in the skin of an apple that sometimes happens when one is trying to break it in two. Histologically the periosteum is inseparable from the unossified portion of the bone so that at the margins it cannot be stripped up, hence the hemorrhage is always limited by the margins of the bone over which it occurs; e.g., right or left parietal, occipital, frontal, etc. It may occur over more than one bone at one time and Ehrenfest quoted a report of a case in which it extended across the midline in a child with the sutures firmly united.

The process is a collection of blood beneath the periosteum. This clots and usually a fair proportion is absorbed. However, if large enough, organization and bone formation occur in the mass which in time disappears. In the type associated with fracture of the cranial bones there may be underlying brain damage, but this is relatively infrequent. When bone formation begins to occur around the edges it may be difficult to distinguish from depressed fracture of the skull. The only treatment necessary is to protect the lesion from infection. Because of the possibility of introducing infection and the danger of increased bleeding, it is inadvisable to aspirate the swelling. If left alone it will disappear in due time. There is no prophylaxis for this condition because it occurs in normal as well as instrumental deliveries.

Cutaneous and Subcutaneous Hemorrhages.—There are two kinds of cutaneous and subcutaneous hemorrhages. The one type is the large ecchymotic area and the other is multiple small petechial hemorrhages. The latter is usually associated with prolonged difficult labors where there has been some asphyxia present. The larger ecchymoses are associated with trauma caused by forceps or manipulation, such as version and breech extraction or more strenuous methods of resuscitation. In addition, areas of ecchymosis are frequently seen from forceps application or relatively mild trauma as a result of the hypoprothrombinemic state of the infant's blood. One should not necessarily assume if ecchymosis is present that the infant has had rough handling during the process of birth. No treatment is necessary for these hemorrhages as they disappear in the course of time. The prophylaxis consists in avoiding the conditions which are the cause, such as rough handling of the baby and conditions which cause asphyxia, and by giving prophylactic vitamin K to the mother.

Intracranial Hemorrhage (Subdural and Subarachnoid).—Baby N., a premature baby weighing 4 pounds at birth, was admitted to the Hospital for Sick Children at 2 days of age because of blue spells and lack of facilities for the care of premature infants at the place of birth. Physical examination revealed a premature baby with a staring expression and having an up and down nystagmus to the eye. Respiratory movements were shallow. Fontanels were both open but not bulging. The baby had more blue spells associated with which it coughed and vomited some blood-tinged fluid. Red blood count was 5,800,000; hemoglobin 125 per cent; blood smear, normal. Prothrombin time was estimated and found prolonged. Vitamin K was administered. The blue spells continued in spite of oxygen being given, and the baby died the day after admission at 3 days of age.

At post-mortem examination hemorrhage was found in both lungs. In addition to that there was a large subdural hemorrhage below the tentorium, and both of the free edges of the tentorium were completely torn across. This was the site from which the hemorrhage had arisen. In addition to this there were extensive areas

of subarachnoid hemorrhage over both cerebral hemispheres and some in the cerebellum.

Certain interesting features of this case are, first, the signs of increased intracranial pressure, such as bulging fontanel, were absent; second, the association of moderately marked hypoprothrombinemia with a severe trauma of the brain, causing a bilateral tear of the tentorium.

There are three common sources for gross subdural hemorrhage: (1) bleeding from veins torn lose from the superior longitudinal sinus caused by overriding of the bones of the skull in the moulding process; (2) bleeding from tears of the tentorium or falx; (3) hemorrhage from a tear of the intracerebral veins, particularly the great vein of Galen.

The older literature emphasizes the overlapping of the parietal bones with tearing of the tributaries of the longitudinal sinus as the largest cause of intracranial hemorrhage. However, with the change made in the method of autopsy devised by Beneke in 1910 by which the membranes falx and tentorium were left intact and both cerebral hemispheres removed separately, it has been shown that by and large the commonest cause is tearing of the leaves of the tentorium. On its free margin it carries large veins which, when torn quickly, empty a considerable amount of blood into the subdural space. When one considers the type of strain that takes place in the cranium of a baby during birth, it is easy to understand why the tentorium is frequently torn. In order to pass through the birth canal, particularly if the pelvis is small, the transverse diameter tends to decrease, causing an increase in the longitudinal diameter. In other words, the head of the baby is elongated and this pulls on the falx and its attachment to the tentorium. This of course is more marked with the use of the instruments where increasing strain and traction are applied. It is also present in precipitous deliveries and more prone to occur with premature babies. In the latter the cranial bones are not sufficiently developed to act as a dilating force and so the elongation of the head is more marked. Crothers has shown that there is great tension on the tentorium in breech deliveries. Ehrenfest states that the use of twilight sleep predisposes to intracranial hemorrhage because of the prolonging of the second stage and also the more frequent use of forceps. Rydberg emphasizes the point that during labor the brain is subjected to remittent pressure which stops the circulation in the veins and makes them more prone to injury. Ford, in discussing hemorrhage from the vein of Galen, points out that this vein runs from one area of comparative freedom of motion in the brain substance to a fixed position in the tentorium and in the latter position it is subjected to strain, kinking and tearing.

The symptoms and signs of gross intracranial hemorrhage are fairly marked. The child may be stillborn or born with asphyxia livida or pallida. The latter, as shown by Crothers, is due to vasomotor collapse from medullary injury. Difficulty in resuscitation is a common symptom and when respiration is established it is sluggish and shallow. Occasionally the child is restless, but more frequently he is drowsy. Attacks of cyanosis occur. Twitchings or convulsions and a loud shrill cry may be observed if the hemorrhage is over the cortex. Rigidity and retraction of the head and nystagmus and unequal pupils may be seen. The fontanel occasionally is bulging, but this should not be depended upon. Difficulty in getting the child to nurse and irregularities of heart rate are common.

Lumbar puncture will frequently reveal a bloody spinal fluid. This in itself does not indicate intracranial hemorrhage because the blood may come from damage to the venous plexus overlying the cord. Microscopic examination, however, will reveal crenated and broken down cells when the blood has been there for some time, as in intracranial hemorrhage. Xanthochromia of the supernatant fluid is suggestive of intracranial hemorrhage, but yellow staining is also present with icterus of the newborn infant.

Lumbar puncture has been advised by some and opposed by others as a method of treatment of intracranial hemorrhage. Those who advise it state that the intracranial pressure is relieved in this way. Those opposing say that it leads to further hemorrhage. In any event the general care is that used in the treatment of shock. The child should be handled as little as possible, kept warm, and watched very closely. Feeding should be done with as little disturbance as possible; gavage is often the solution. Some advise keeping the head elevated in order to minimize the hemorrhage. Others lower it in order to allow the mucus to drain from the trachea which is always a marked factor in intracranial hemorrhages. The air passages must be kept free. Because of the poor or shallow respiratory movements it is advisable to administer oxygen. Transfusion of whole blood is advocated by many and also vitamin K administration because of the lowered prothrombin which is natural for the newborn state.

The course and prognosis depend largely on the site and extent of the hemorrhage. In my own experience, if the patient does not die at the time, very few of the cases diagnosed as intracranial hemorrhage have any recognizable sequelae. Most of the mental-defect and paraplegic patients that have been seen were not diagnosed as intracranial hemorrhage at birth, and in going into the history asphyxia of the brain or cerebral agenesis would seem more likely causes.

The more common site for hemorrhage is from the tentorium. The great majority of these are fatal at birth or within a few days, particularly if the blood clot forms below the tentorium, where it affects the medulla. Hemorrhage from the vein of Galen and intracerebral hemorrhage are practically all fatal. The supratentorial hemorrhages over the cerebral cortex are more likely to survive. The large majority of these absorb and disappear. It is believed that some of them cause a softening and destruction of the underlying brain tissue. This leads to paraplegias and mental defectives. Occasionally large subdural hemorrhages partially organize with membrane formation, then break down and bleed again, forming the subdural hematoma.

The prophylaxis of intracranial hemorrhage is essentially an obstetric problem. However, the pediatrician can make and has made a contribution in the prevention of rachitic bony deformities of the pelvis which lead to difficult delivery. The improper and unnecessary use of forceps should be discouraged, and the same applies to drugs, such as pituitrin and ergot, which cause contraction of the uterus. The use of twilight sleep and hypnosis makes the likelihood of instrumental interference more probable so that the unnecessary use of these must be avoided. Administration of vitamin K to the mother as a prophylactic measure is advisable. This point will be amplified in discussions by other members of the group.

Visceral Hemorrhage.—Baby B. was admitted at 7 days of age with a birth weight of 7 pounds. The infant was delivered with extreme difficulty by breech extraction, and forceps were used with considerable traction. There was difficulty in resuscitation necessitating artificial respiration for a long period (the type used not being stated), and the breathing when established was very shallow. A hematoma appeared under the chin. The child did not move the right side of the body and appeared quite pale, drowsy, and listless. On admission he was drowsy and appeared in a state of shock. A hematoma was present under the chin. A mass the size of a large orange was found in the left side of the abdomen merging with costal margin above and having lower boundary in the pelvis. The abdomen also gave a crepitant sensation on palpation. A diagnosis of left massive suprarenal hemorrhage and hemorrhage into subcutaneous tissues of the neck was made. The child was transfused twice with no improvement and died at 10 days of age. At postmortem the following anatomic findings were diagnosed: hematoma of cervical region, massive left suprarenal hemorrhage and small right suprarenal hemorrhage, hemorrhages into lungs, intracranial hemorrhage, subdural and subarachnoid. This case was reported previously by Dr. Erb and myself.

Hemorrhage of this type occurs from the lung, liver, and suprarenal. The suprarenal is one of the more common sites and in most texts a separate section is taken for the description of this type. Difficult delivery and vigorous methods of resuscitation are the main causes of visceral hemorrhage.

There are factors which predispose the suprarenal gland to hemorrhage in this period. During the first two weeks the cortex comprises most of the gland and is very vascular at this time. Because of the increased vascularity and friability of the glands, they are very easily damaged with hemorrhage as a result. The other factors which enter into etiology are (a) lowered prothrombin of the blood; (b) difficult delivery, particularly breech; (c) Schultz method of resuscitation; (d) increased pressure in the inferior vena cava and suprarenal vein; (e) and asphyxia which will be developed by Dr. Clifford later as an important factor in the production of this condition.

The pathologic changes may vary from a small hemorrhage to such large ones that the whole gland is destroyed. In the larger hematomas in which the patient survives calcium is usually laid down during the organization process. It is frequently bilateral.

The clinical course has been described as follows: shock, listlessness, refusal of food, rapid respirations, rapidly developing anemia, bogginess of the abdomen with or without bluish discoloration, and occasionally a palpable mass.

In treatment one attempts to combat shock and anemia. This is done by transfusion. Arnold reported cures by this method. Evacuation of the clot has been carried out by some but it is not necessary and only subjects the child to further trauma. If the adrenal glands are not both completely destroyed, the child may still live if the shocked state is overcome. However, the outlook is poor in the majority.

As this condition is produced by difficult delivery, particularly breech extraction, and strenuous methods of resuscitation, both of these should be avoided if possible as a method of prevention. Asphyxia of the baby should be avoided if possible, and prophylactic administration of vitamin K is of definite value.

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Hemorrhages of Asphyxial Origin

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The importance of asphyxia in initiating symptoms of hemorrhage in the newborn infant does not appear to be generally appreciated. In 1937 I reviewed sixty-nine cases diagnosed as "hemorrhagic disease" at the Boston Lying-in Hospital and

found that 50 per cent of these patients had been sufficiently asphyxiated to have required artificial resuscitation at birth. In addition, in many of these resuscitated infants there had been gross abnormality of the fetal heart rate and the passage of meconium during labor. The total group of sixty-nine cases have been subdivided in Table I according to the location of the major hemorrhage and the incidence of a history of asphyxia.

TABLE I

	NUMBER OF CASES	PER CENT WITH EVIDENCE OF FETAL ASPHYXIA
Cases with gastrointestinal hemorrhage	41	38
Cases with massive adrenal hemorrhage	9	78
Cases with asphyxial type of intracranial hemorrhage	10	60
Cases with traumatic type of intracranial hemorrhage but with spontaneous hemorrhage elsewhere	9	78

In a recent publication the pathologic changes induced by asphyxia were described as congestion, edema, hemorrhage, and tissue degeneration. It was pointed out that these changes might involve every organ and tissue of the body. It was also stated that while the association of petechial hemorrhage and asphyxia was well known, the importance of extensive asphyxial bleeding in other locations should be stressed. It was also suggested that much of the gastrointestinal, pulmonary, liver, and intracranial hemorrhage might be of asphyxial origin.

MELENA VERA; HEMATEMESIS; UMBILICAL, MUCOUS MEMBRANE, SUBCUTANEOUS AND GENITOURINARY HEMORRHAGE OF ASPHYXIAL ORIGIN

Intrauterine Melena Vera.—The mother of this patient started mild labor pains about seven weeks from term, ruptured her membranes, and began passing old brown blood. During the next twenty-four hours a continuous slight ooze was present, increasing sufficiently to run down the leg with each pain. In the second twenty-four hours the blood loss continued as before. The mother's general condition was excellent, the fetal heart rate was between 120 and 132, and delivery took place normally without anesthesia. The infant weighed 4 pounds, 12 ounces. He was limp and would not cry although he breathed spontaneously. He was thickly covered with sticky old blood.

The amniotic sac contained a large amount of the same bloody material. The placenta appeared to be necrotic and was so friable it pulled apart at the slightest manipulation. The umbilical cord was stained a deep green and was so friable that great care had to be exercised when it was tied to prevent its being cut right through.

At the age of 1 hour the baby was hypotonic and stimulation produced only a weak whine. His color was good and he was universally covered with this jamlike layer of blood.

Because the skin felt cold and clammy his rectal temperature was immediately taken. It was 96° F., but of more interest, the thermometer bulb was covered with a large amount of sticky, deep red, mahogany-colored old blood identical to that covering the skin. Intramuscular vitamin K was given at once. The infant was not suffering from loss of blood; the red blood count was 4,999,000 the first day and 4,200,000 on the third day.

The nurses were warned that the baby would have bloody stools, but not a single dejection took place until the infant was 48 hours of age. Then the diapers con-

tained large quantities of old red changed blood in successively decreasing amounts but no recognizable amounts of meconium. Nothing more was done in the way of treatment and the infant's course was entirely uneventful.

It is certain that had we not obtained the evidence of melena on the thermometer at birth we would have had an "emergency call" from the hospital forty-eight hours later that the infant had developed hemorrhagic disease.

It is my belief that because of the degenerative changes in the placenta the fetal circulation became embarrassed and the infant became asphyxiated in utero. He first emptied his colon of meconium, this mixed with the amniotic fluid in sufficient strength to stain deeply the umbilical cord. Furthermore, no recognizable meconium was passed after birth. Later he developed melena vera in utero, staining himself and the amniotic fluid with the old blood. It was this material that had escaped when the membranes ruptured.

Melena Vera.—The mother of this patient was one week overdue when she began passing a moderate number of blood clots. The fetal heart rate was between 144 and 120. The baby, weighing 6 pounds, 1 ounce, was delivered normally after eighteen hours of labor. The cord was found about the neck, and the infant did not breathe until after artificial resuscitation.

At the age of 4 days the baby became pale and listless and nursed poorly. He passed a large amount of blood in the stools. The red blood count was 3,000,000; bleeding time, eight minutes; clotting time, three minutes. A blood transfusion was given. The infant continued to pass tarry stools until five hours later when he passed another large stool, this time of fresh blood. After a second transfusion the convalescence was uneventful.

Hematemesis.—The mother of this infant was one week past term. One-half hour before delivery the fetal heart rate was 112 and difficult to hear. Fifteen minutes before delivery it was 80 and irregular, and large amounts of meconium were being passed. At delivery the fetal heart rate was 60. The head was delivered by low forceps. The infant was not only covered with meconium but he had also aspirated a considerable quantity of this substance. Artificial resuscitation was required. The birth weight was 7 pounds, 2 ounces.

At 24 hours of age the infant was pale and apathetic with a slight elevation of temperature. On the third day the baby was still pale and listless and had developed a left internal strabismus. The red blood count was 4,400,000; hemoglobin, 75 per cent; bleeding time, one and one-half minutes; coagulation time, three and one-half minutes. The infant vomited old blood twice and later vomited a large amount of old blood.

A transfusion was given and the convalescence was normal.

Subcutaneous and Mucous Membrane Hemorrhage.—A 7-pound infant was delivered by low forceps at full term with the cord twice around his neck. The fetal heart had been very slow and the infant could not be made to breathe at birth until after five minutes of artificial resuscitation. Slight ecchymosis had been present in both cheeks since birth, but on the fifth day a marked hemorrhagic swelling appeared in the right cheek and a smaller one in the left. The gums also began to bleed at this time. The red blood count was 3,780,000; hemoglobin, 75 per cent; bleeding time, five minutes; clotting time, two and one-half minutes.

Because of the low red count and possible internal bleeding, the baby was transfused. His convalescence was uneventful.

Genitourinary Bleeding.—An infant weighing 7 pounds, 4 ounces was delivered normally one week past term. The fetal heart rate had been between 100 and 140. Four minutes of artificial resuscitation had been required at birth. On the fourth day he vomited old blood. The red blood count was 4,500,000; hemoglobin, 75 per cent; bleeding time, four minutes; clotting time, eleven minutes. He again vomited, this time fresh blood, and passed a large amount of blood-stained urine.

A transfusion was given. The next sample of urine was grossly bloody with the sediment loaded with red blood cells. There was no further bleeding and the convalescence was uneventful.

Umbilical Hemorrhage.—The mother of this patient was at full term; her cervix had been fully dilated for two and one-half hours. The occiput had reached the right transverse position and had there become arrested. The fetal heart dropped from 180 to 80. The patient was anesthetized, the fetal head rotated, drawn down with traction rods and delivered with the blades in place. The shoulders were delivered with difficulty after the cord, which was tightly wound around the neck, had been divided. At birth the infant was covered with meconium but did not require resuscitation.

The birth weight was 7 pounds, 11 ounces. On the third day the baby was pale and began bleeding bright blood from the base of the cord and umbilicus. The upper part of the cord was well tied and dried up. Numerous petechial hemorrhages had been observed at birth over the head and in the mouth and ecchymotic areas noted over the face.

A transfusion was given. The convalescence was normal.

In the series of 69 cases diagnosed as hemorrhagic disease referred to previously, 41 were in the group with melena vera, hematemesis, umbilical, subcutaneous, mucous membrane or genitourinary bleeding. In this group, 15, or 38 per cent, were found to have an obstetric history suggesting intrauterine asphyxia. Every one of these 15 was asphyxiated at birth, requiring artificial resuscitation. Seven showed abnormal variations in the fetal heart rate, 5 passed meconium during labor, 3 had cords about their neck, 3 had prolonged second stages of labor with the head on the perineum, while 3 of the mothers had hemorrhage from the placenta.

This evidence at least suggests that asphyxia may be an important factor in initiating the primary break in the integrity of the vascular tree, thus permitting the escape of the hypoprothrombinemic blood of the newborn. The prevention of this type of hemorrhage should begin with the prevention of asphyxia wherever possible. Given a history of fetal asphyxia, we should be forewarned to watch for evidence of bleeding in the newborn.

I think we can accept as proved the fact that vitamin K can control the hypoprothrombinemia of the newborn if administered to the mother at least three hours before delivery or if given directly to the infant. If we can make the assumption that this correction of the hypoprothrombinemia will prevent or minimize bleeding from injured blood vessels, then the time this protection is needed is during the period of possible injury or during the actual birth process. Therefore, to be most effective the prophylactic treatment with vitamin K must be given the fetus via the mother sufficiently long before birth to afford protection during this crucial period. If vitamin K has not been given the mother, it should be administered as soon after birth as possible, but under these latter conditions it is not fair to condemn vitamin K for failure to prevent hemorrhages that have already occurred.

ADRENAL HEMORRHAGE

In the sixty-nine cases of hemorrhagic disease that were studied, there were nine examples of massive adrenal hemorrhage. The obstetric histories of these cases of adrenal hemorrhage were striking in their similarity. Some mechanical difficulty in delivery was encountered in every case. One-half of the babies weighed 9 pounds or more. Cephalopelvic disproportion, difficulty in delivering the shoulders in three cases, dystocia in four cases, abnormal position of the fetal head, transverse arrests, and the umbilical cord about the posterior shoulder are examples of the problems that were encountered. Accompanying these difficulties, in every case but one, was gross variation or disappearance of the fetal heart. In seven of the nine cases there was

difficulty in resuscitation at birth. There was one further point in common. In addition to the intrauterine asphyxia and asphyxia at birth, the anoxemia was prolonged into the neonatal period as the result of either pulmonary or cerebral injuries. An example of this type of hemorrhage follows.

The mother of the patient was two weeks beyond full term. She had a total labor of twenty-nine hours during the last four of which her cervix was fully dilated. The fetal head was arrested in the mid-position with the right occiput posterior. The fetal heart rate ranged between 128 and 176. The head was rotated by forceps to a right occiput anterior. Extraction was then performed easily. The infant weighed 9 pounds, 13 ounces and required artificial resuscitation.

After birth the infant's cry was shrill and respirations were jerky. The color was cyanotic. The baby's course for the first five days was not remarkable except for inspiratory stridor and occasional attacks of mild cyanosis. The anterior fontanel became rather tense. On the eighth day of life a large mass was discovered in the left flank, extending from the costal margin into the pelvis and across to the umbilical line. The baby was active but pale with a red blood count of 2,300,000 cells per cubic millimeter and a hemoglobin of 45 per cent. The bleeding time was one-half minute and the clotting time was five minutes. The diagnosis of a massive adrenal hemorrhage was made. A blood transfusion was given at once. On the eleventh day the red count was 3,420,000 and the hemoglobin, 55 per cent. On the fourteenth day the red count and hemoglobin were the same, and the baby was normal except for his pallor and the presence of the mass. The convalescence was not remarkable from this point on.

Contrary to the 100 per cent mortality usually expected with massive adrenal hemorrhage, four of our nine patients survived. The progress depends on their early recognition and treatment by blood transfusion. We have not encountered this condition since the introduction of vitamin K but here again, since the initial injury takes place during birth, the prophylactic treatment must be given through the mother if the infant is to be protected at the critical time. It is also reasonable to suggest that infants delivered following difficult or abnormal labor, particularly if coupled with abnormality of the fetal heart rate or asphyxia at birth, should be given vitamin K at once. They should be observed closely for signs of hemorrhage and given a blood transfusion to replace unusual blood loss.

INTRAVENTRICULAR, SUBARACHNOID, SUBDURAL AND INTRACEREBRAL HEMORRHAGE

A 21-year-old primipara developed an intractable *B. coli* pyelitis in the sixth month of her pregnancy. Her illness required three hospital admissions. She received sulfathiazole or sulfanilamide or both at each admission. Her entire course was complicated by severe anemia, the red blood count ranging between 1,600,000 and 2,900,000, and she received ten blood transfusions before delivering normally at full term.

At birth the male infant, weighing 5 pounds, 1 ounce, was asphyxiated and failed to breathe until after artificial resuscitation. The placenta and membranes were normal except for meconium staining. Vitamin K (3.2 mg. hykinone) was immediately administered intramuscularly and the infant admitted to the pediatric nursery. The infant was placed in an oxygen bed and became severely cyanotic when removed. His cry was shrill, the muscles were spastic, the lungs were dull throughout to percussion, the fontanel was not tense, and the head circumference was 32.3 cm.

On the second day the initial dose of Vitamin K was repeated, cyanotic attacks took place in spite of continuous oxygen therapy, the shrill cry and muscular rigidity continued, two convulsions took place, and the anterior fontanel became tense. Two lumbar punctures produced 10 and 6 c.c. of grossly bloody fluid and reduced the

fontanel tension. The infant's red blood count was 4,000,000 and hemoglobin, 14.8 Gm.

On the third day the baby was comatose, the muscles were still spastic, a left internal strabismus was noted, and the fontanel was again full although the head circumference was still 32.3 cm. By lumbar puncture, 0.5 c.c. of grossly bloody fluid was removed. A cistern tap was attempted unsuccessfully. No fluid was obtained by right subdural, right ventricular, and left subdural punctures. A left ventricular tap produced 2 c.c. of a grossly bloody fluid resembling that previously withdrawn.

From the fourth through the eighth day the baby's general condition rapidly improved. His color became normal, the lung percussion note normal, and oxygen no longer needed. The muscle tone became normal, the absent moro reflex returned, and the anterior fontanel remained of normal tension.

The first eight days just described represent the first phase of this infant's illness and was interpreted as the result of intraventricular and subarachnoid hemorrhage of asphyxial origin. It was felt that the bleeding had been minimal and the immediate prognosis excellent.

On the ninth day the infant's condition suddenly changed and he entered his second phase. Within twenty-four hours the fontanel became very tense, the sutures separated, and the head increased over 2 cm. to 34.6 cm. in circumference. The cry again became high-pitched and the infant began vomiting. Lumbar puncture produced 60 c.c. of an entirely different type of fluid under increased pressure. The fluid consisted of old chocolate-colored blood mixed with spinal fluid. The fluid at the end of the drainage was the same type as that at the start. The explanation of these findings was that an encapsulated cerebral hematoma had ruptured into the ventricular system. The drainage reduced the fontanel tension to normal and the head circumference to 33.6 cm.

From the tenth through the thirteenth day daily lumbar drainage was required to control the fontanel tension and the head size. The fluid continued to be chocolate-colored but the amount of old blood sediment gradually diminished. At this time the infant was transferred for four days to the Children's Hospital for the drainage of a gluteal abscess formed at the site of a vitamin K injection. While there, frequent lumbar and subdural punctures were performed and large amounts of fluid removed from the subdural region.

When the infant returned to the Boston Lying-in Hospital at 18 days of age, the fontanel was still tense. Lumbar puncture produced 30 c.c. and left subdural tap 15 c.c. of orange, deeply xanthrochromic fluid free from red blood cells. From this point to the thirty-fifth day, drainage was required less and less frequently; the fluid from both subdural and lumbar regions progressively cleared until on the last day only 4 c.c. of crystal-clear fluid was obtained from the left subdural tap. The head circumference was 36 cm. At this point the baby was transferred to the neurological service at the Children's Hospital where burr holes revealed the presence of a thin subdural membrane. On the forty-second day a bone flap was turned down on the left and a section of very thin, pigment-containing subdural membrane was removed.

The subsequent course in the hospital was uneventful; the ultimate prognosis is for the future to determine.

This case history further emphasizes the fact that if vitamin K prophylaxis is to be effective it must be administered to the fetus via the mother. When the obstetric history suggests possible injury to the fetus, vitamin K should also be given the infant immediately at birth.

In all types of bleeding the red blood count and hemoglobin must be followed closely, and whenever the blood loss approaches the critical level, blood transfusion should be given.

In treating the various types of intracranial hemorrhage, we try to drain all blood from the subarachnoid and ventricular spaces by repeated lumbar punctures until crystal-clear fluid is obtained. The lumbar drainage is also performed frequently enough to keep the intracranial pressure under control. Evidence of abnormal intracranial pressure is given by palpation of the anterior fontanel tension and separation of the sutures as well as by measuring the rate of increase in the head's circumference and clinical symptoms.

When insufficient fluid can be withdrawn from the lumbar space to relieve the intracranial pressure or when the lumbar puncture results in a "dry tap," the presence of either a block or hemorrhage in the subdural space is suspected. A cistern tap is then attempted and if this succeeds in relieving intracranial pressure, this route is used until the lumbar approach opens up.

If the cistern tap fails to relieve the pressure it must then be determined whether the pressure is due to blocked drainage from the ventricles or to hemorrhage confined to the subdural space. In the latter case subdural taps may produce old blood, usually under increased pressure and free from spinal fluid. Under these circumstances the evidence points to a true subdural hematoma that is treated by frequent tapping followed by neurologic exploration to remove as much of the clot as possible and to remove a part of the membrane that may be formed under these conditions. Unless this surgical procedure is performed, the membrane may either result in chronic pachymeningitis hemorrhagica interna or produce a hydrocephalus. The situation when the subdural tap produces old blood mixed with a large amount of spinal fluid will be considered later.

If the subdural tap fails to reveal the presence of abnormal fluid, the intracranial pressure must be controlled by direct ventricular puncture until such time as drainage can be accomplished by the cisternal or lumbar route. Under all conditions ventricular taps are performed with reluctance for fear of rupturing surface blood vessels and adding to the cerebral, subarachnoid, or subdural bleeding, and because the pathway of the needle may serve as a route by which the ventricular fluid, under pressure, may pass directly into the cerebral subarachnoid and into the artificially opened subdural space. In the case history of the patient with ventricular and subdural hemorrhage just reported, this is suggested as the way the subdural space became distended with old blood and cerebrospinal fluid.

Once the subdural space becomes filled with blood or blood and spinal fluid and unless this fluid can be successfully drained off by repeated subdural taps, the presence of this material may result in the formation of a membrane. Unless all signs of increased intracranial pressure disappear and the fluid clears and disappears from the subdural space, we believe the infant should have burr holes in his skull to prove the presence or absence of a membrane. If a membrane is present a flap should be turned down and a liberal section of the membrane removed surgically.

If the cerebrospinal fluid block already described should persist, a surgical exploration should be undertaken for its relief.

While the patient with an intracranial hemorrhage is being drained, fluids should be forced to increase the flow of cerebrospinal fluid in the hope of diluting and washing out the old blood and thus prevent block formation.

Hypoprothrombinemia and Hemorrhage in the Newborn Infant

W. W. Waddell, Jr., Charlottesville, Va.

Most of the confusion concerning hemorrhage in the neonatal period centers on the definition of this unsuitable and unfortunate term. Clinicians have in the past been unable to agree among themselves as to what should and should not be included under this classification; so much so that few reported series are comparable from the standpoint of incidence, sites of bleeding, and mortality rate. Interest

in this particular clinical syndrome has been greatly increased as the result of recently published data concerning etiology, prevention, and treatment which are not altogether compatible with past ideas on this subject.

It would seem necessary to review the commonly expressed conceptions concerning the incidence of hemorrhagic disease, sites of bleeding, classification, mortality rate, prevention, and treatment. Until we can agree as to what is or is not hemorrhagic disease, its incidence will never be determined. Sanford found only three instances of hemorrhagic diseases in 9,000 newborn infants while Clifford considers the incidence of from 0.3 to 0.5 per cent the more correct figure. In reviewing the records at the University of Virginia Hospital, we find 32 (0.5 per cent) cases in 6,290 infants. We include only those cases which showed a prolonged clotting time.

Attention has been called to the increased incidence of hemorrhagic disease in the winter and spring months. Generally this has been thought to have no real significance. Such an incidence was found to be present in our own small series. At the University of Virginia Hospital a similar seasonal incidence occurs in hypoprothrombinemia of the newborn. Lawson and I have further shown that an identical seasonal incidence occurs in the death rate from intracranial hemorrhage for the United States as a whole. This study covered the registration area of the United States for a ten-year period. During this period approximately one-third more infants died from intracranial hemorrhage during the winter and early spring months than in other calendar months. Not only was this true for the ten-year period but for each year of the ten-year period.

Concerning sites of bleeding I would state simply that bleeding may occur anywhere in the body from one or more sites. The relative frequency in any particular site will again depend upon one's conception of what is or is not hemorrhagic disease. Snedeker lists the following bleeding sites in 358 cases of hemorrhagic disease from the Boston Lying-in Hospital and the Infant's Hospital: Purpura, intracranial, forceps marks, tongue-tie cut, tongue, circumcision wound, retracted foreskin, umbilicus, adrenals, vagina, gastrointestinal tract, renal, intra-abdominal, liver, gums, sclerae and conjunctiva, hemothorax, orbit, and external auditory meatus. In some of these instances bleeding was obviously precipitated by trauma. It is pleasing to note that he includes trauma as an "etiologic factor of importance." This is in distinct contradiction to the classification insisted upon at the Boston Lying-in since Townsend published his original report and gave us the name of hemorrhagic disease.

Concerning the etiology of hemorrhagic disease, two factors have long been considered of great importance. Namely, failure of the blood to clot properly and some defect in the vessel wall allowing the escape of blood into surrounding tissues. Rodda was the first to observe the prolonged clotting time occurring during the first week of life and insisted that this finding must be present before the diagnosis of hemorrhagic disease could be made. Instances of spontaneous hemorrhage of a severe degree without disturbance in the clotting mechanism have been exceedingly rare in my experience. All of us will agree that prolongation in the clotting time in the first week of life is a common occurrence. Recent data have amply confirmed the opinion expressed in no uncertain terms by Whipple as far back as 1913 that prothrombin deficiency was the reason why the blood failed to clot properly in cases of hemorrhagic disease.

Early in 1939 we reported the cases of two infants with marked prothrombin deficiency. In one infant there was, in addition, unnatural bleeding. Following the administration of vitamin K concentrate, the prothrombin level promptly returned to a safe level and the bleeding was promptly checked. On this evidence we suggested that vitamin K might prove useful in the prevention and treatment of hemorrhagic disease. Further studies followed promptly, and we have since described the unusual frequency with which hypoprothrombinemia occurs and its prompt and con-

stant prevention when vitamin K is administered to mother and infant. It is our belief that the immediate cause of the disturbed clotting mechanism in hemorrhagic disease is the result of prothrombin deficiency which in turn is the expression of vitamin K deficiency in the infant. We also believe that instances of hemorrhagic disease associated with prolonged clotting time would not occur in infants adequately protected with vitamin K. Obstetric trauma in some instances is but the precipitating factor in intracranial hemorrhage, thus initiating hemorrhage in an infant that is by reason of prothrombin deficiency a potential bleeder. Vitamin K should prove a much needed therapeutic agent.

Recent literature on this subject is fairly extensive and has in general with one exception added strong support to this conception of the etiology prevention and treatment of hemorrhagic disease. Certain objections can and will be raised to this general concept, some of which may well be discussed at this time. It is freely admitted that there is no known prothrombin level below which bleeding occurs. This has led to the suggestion that some additional factor such as capillary damage must be present before prothrombin deficiency can result in hemorrhage. It is equally reasonable to assume that without disturbance in clotting mechanism any such additional factor is in turn unable of itself to precipitate hemorrhage. I am unaware of any reported case of hemorrhagic disease occurring in an infant adequately protected with vitamin K. The prompt cessation of hemorrhage in suitable cases following vitamin K therapy with the invariable rise in prothrombin level does not suggest any fault with containing vessels. It can equally well be said of hypoprothrombinemia of obstructive jaundice that all cases even under the insult of surgical trauma do not bleed at the same prothrombin level, yet the effectiveness of vitamin K in such conditions is a proved and accepted fact.

It would seem undoubtedly true that hypoprothrombinemia of the newborn is more prevalent in certain sections of the country than in others. It would be surprising if such were not the case if it is in fact a deficiency disease. We can certainly agree with the statement that hemorrhagic disease does not occur with the same degree of frequency in all of our medical centers and the same can be said of beriberi, scurvy, pellagra, and rickets. When we know the answer as to why hypoprothrombinemia occurs in some infants and not in others and particularly why it has a seasonal incidence, this question will doubtless be answered.

The question as to whether or not vitamin K therapy has, to any real degree, been instrumental in the prevention and treatment of hemorrhage in the neonatal period would seem well answered in current literature. It would seem necessary to establish beyond a question of doubt the efficiency of vitamin K in a field of such importance as the one now under discussion. Previous to the time when prophylactic vitamin K therapy became routine in our nursery, our house staff was frequently being called to stop troublesome hemorrhage. These conditions no longer exist. Hemorrhage other than that due to trauma has become a negligible factor. We have not found it necessary to give a single transfusion for the purpose of checking hemorrhage or because of blood loss in over 1,600 infants treated with vitamin K.

Any further discussion of hemorrhagic disease having to do with classification, symptoms, and mortality may well come later.

SUMMARY

Certain facts concerning hemorrhagic disease which in the past have been unexplained now seem quite clear: (1) That hypoprothrombinemia is the immediate cause of prolonged clotting time can no longer be questioned; (2) the fact that marked prothrombin deficiency is usually corrected by the fifth day is striking evidence of its etiologic relationship to hemorrhagic disease; (3) the seasonal in-

cidence of hemorrhagic disease which has received scant notice in the older literature assumes new importance and would seem adequately explained by an identical seasonal incidence in the frequency of hypoprothrombinemia; (4) hypoprothrombinemia and associated prolonged clotting are efficiently prevented by administration of vitamin K; (5) hemorrhage associated with hypoprothrombinemia and prolonged clotting time is promptly controlled by administration of vitamin K; (6) recent data confirm the suggestion that hemorrhagic disease with prolonged clotting time will not occur in any infant adequately treated in a prophylactic fashion. In support of this statement the data in Table I speak for themselves and cannot be interpreted as a mere coincidence. These are personal communications from Drs. Clifford,* Eastman, Poncher, Snelling and Grossman. To these we add our own experience.

TABLE I

AUTHOR	NUMBER OF TREATED CASES	INCIDENCE OF HEMORRHAGIC DISEASE
Clifford (Boston Lying-In)	1,023	0
Eastman (The Johns Hopkins)	1,014	0
Poncher	123	0
Snelling	150	0
Grossman	250	0
Waddell (University, Va.)	1,581	0
Total	4,141	0

It would be foolish to suggest that an occasional incidence of serious and unexplained hemorrhage will not occur. It seems likely that such occurrences will be so infrequent as to cause us little concern. In the future as in the past some of them will doubtless serve as a reminder of the need for more adequate case study.

CONCLUSION

Each member of the panel was requested to submit his personal definition of "hemorrhagic disease of the newborn" before this meeting.

DR. W. W. WADDELL, JR.—I would insist that the term "hemorrhagic disease" be used for only those cases which show prolonged clotting time.

DR. C. E. SNELLING.—Hemorrhagic disease to me is a state of the newborn baby which is characterized by a decrease in prothrombin content of the blood to a level at which if the blood vessels are damaged in any way, continuous slow bleeding will occur. I do not believe that the bleeding and clotting times necessarily have to be changed to an abnormal degree with the diagnosis, but I do feel that the diagnosis cannot be made if the prothrombin time is normal. As I stated previously in my first published report on this subject, there are many infants with a prothrombin level of the blood which is low and no bleeding, and I concluded that there must be some other factor which initiates the bleeding. The lowered prothrombin time of the blood keeps it going.

*THE EFFECT OF VITAMIN K ON BLEEDING IN THE NEWBORN AT THE BOSTON LYING-IN HOSPITAL (CLIFFORD)

	1,023 CASES PROPHYLACTIC "K"		1,945 CASES CONTROLS	
	NUMBER OF CASES	RATE PER 1,000	NUMBER OF CASES	RATE PER 1,000
Hemorrhagic disease	0	0	7	3.5
Intracranial hemorrhage	3	3	8	4.0
Cephalohematoma	11	11	9	4.5
Subconjunctival hemorrhage	16	16	28	14.0

DR. H. G. PONCHER.—Hemorrhagic disease of the newborn should be defined as a condition occurring usually during the first week of life accompanied by spontaneous hemorrhage in any one of several anatomic sites which is associated with a marked diminution of prothrombin in the blood. The clotting time is usually prolonged but need not necessarily be so for the diagnosis to be established. Bleeding time certainly need not.

CHAIRMAN CLIFFORD.—Hemorrhagic disease is the syndrome of spontaneous external or internal hemorrhage accompanied by hypoprothrombinemia occurring in the newborn; excluding that associated with trauma, asphyxia, or some definite disease.

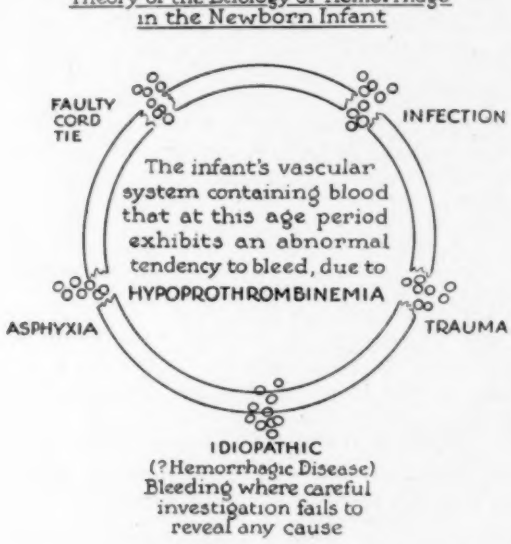
Theory of the Etiology of Hemorrhage in the Newborn Infant
FAULTY CORD TIE
INFECTION
The infant's vascular system containing blood that at this age period exhibits an abnormal tendency to bleed, due to
HYPOPROTHROMBINEMIA
ASPHYXIA
TRAUMA
IDIOPATHIC
(?Hemorrhagic Disease)
Bleeding where careful investigation fails to reveal any cause

Fig. 1.

It was apparent to all that for us to discuss hemorrhagic disease would be pointless since to each of us it represented a different clinical syndrome. On the other hand we found we could discuss the various types of hemorrhage occurring in the newborn in complete agreement just so long as we did not try to decide whether it should be called an example of hemorrhagic disease.

We believe that the present confusion surrounding the problem of hemorrhage in the newborn infant will disappear if the etiologic classification of hemorrhage in Fig. 1 is generally adopted.

We believe that the prophylactic use of vitamin K to control and prevent the hypoprothrombinemia of the newborn should be universally adopted. By this means the infant will be provided with a normal clotting mechanism during any possible period of trauma, asphyxia, sepsis, or other need during the early days of life.

We recommend that every infant should be protected in utero through vitamin K administration to the mother in sufficient amount and in sufficient time before delivery to be effective. There are several methods by which this can be accomplished:

1. Intramuscular or intravenous injection of 3.2 mg. of 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate or the diacetate of the hydroquinone, both of which

are water soluble, to the mother at least four hours before delivery. Repeat every twelve hours.

2. Oral administration of 5 mg. of 2-methyl-1, 4-naphthoquinone in oil at the onset of the first labor pain and repeat every twelve hours until delivery. As labor progresses it may be advisable to change to the water-soluble vitamin K and use the intramuscular or intravenous route of administration as above.

In the normal newborn, normally delivered, there is probably no need to administer additional vitamin K providing the administration via the mother has been effective. In case of doubt in prematurely born infants, after abnormal labor, after fetal asphyxia or artificial resuscitation at birth, 3.2 mg. of water-soluble vitamin K should be given intramuscularly at once. To provide every possible protection in the light of our present knowledge and experience, every newborn baby could well be given vitamin K at birth whether or not there has been previous maternal administration.

Academy News

The following special program has been arranged for the meeting of Region III of the American Academy of Pediatrics, Cleveland, Ohio, May 14, 1942:

The Pediatrician and the War, Lee Forrest Hill, M.D., Chairman, Region III, Presiding.

The Draft, Dr. Robert A. Bier, Major, M.C., U.S.A., Selective Service Headquarters, Washington, D. C.

Procurement and Assignment Service, Dr. E. L. Henderson, Chairman, Fifth Corps Area Committee, Procurement and Assignment Service.

The Office of Civilian Defense, William S. Keller, M.D., Sr. Surgeon Res., U.S.P.H.S., Medical Officer Fifth Region.

The Children's Bureau, Martha M. Eliot, M.D., Associate Chief, The Children's Bureau, Washington, D. C.

News and Notes

Instructions as to the special care of babies in the event of an air raid, based in part on the experience of London and other English cities, have been made public by the American Committee on Maternal Welfare.

In view of the general possibility of air raids on American cities, particularly in the coastal zones, the committee regards it as important that American mothers understand and prepare well in advance for the task of protecting their babies. The committee is composed of the leading medical, public health, nursing and hospital organizations of the country and can thus speak with authority.

The problems of baby and mother in wartime and their safety and well-being under all circumstances, were discussed by experts from all over the Americas at the second annual Congress on Obstetrics and Gynecology, sponsored by the committee, in St. Louis, April 6 to 10.

The Annual Meeting of Region I was held at the Bellevue-Stratford Hotel, Philadelphia, April 1-2, 1942. The first morning was given over to clinics at various hospitals. In the afternoon a symposium on Blood in Infancy and Childhood was held with Dr. Waldo Nelson of Philadelphia, Dr. Alexander Wiener of New York, Dr. George Farrar of Philadelphia, Dr. Philip Levine of Newark, Dr. Ernest Witebsky of Buffalo, Dr. Leandro Tocantins of Philadelphia, and Dr. Charles Doan of Columbus, Ohio, participating.

That evening a discussion of "Pediatrics in the National Emergency" was held with Dr. Alan Butler, Dr. Henry Klein, Dr. Frederick Tisdall, and Dr. Martha Eliot as speakers.

On Thursday morning an "Obstetric-Pediatric" panel discussion was held, and in the afternoon a panel discussion on "Air-Borne Infections," together with three round tables on orthopedic problems, reading difficulties, and dermatologic problems.

On Friday morning there was a panel discussion on the "Early Treatment of Poliomyelitis" at which Dr. Don Gudakunst and Dr. Philip Stimson of New York, Dr. Wallace Cole of St. Paul, and Dr. Alfred Shands, Jr., of Wilmington, Delaware, participated. Round tables on "Endocrines," "Everyday Training of the Child," and "Chemotherapy" were held simultaneously.

Thursday noon was given over to a number of committee luncheons and the banquet was held on that evening. There was a large attendance and the details of the meeting were excellently carried out by the local committee in charge.

Book Review

Neural Mechanisms in Poliomyelitis. Howard A. Howe, M.D., and David Bodian, Ph.D., M.D., New York, 1942, The Commonwealth Fund, pp. 234. Price $3.50.

In this volume Howe and Bodian have brought together and discussed the experimental, pathologic, and other observations on poliomyelitis which they have made during the past few years, much of it previously published last August in the Bulletin of the Johns Hopkins Hospital. Their work is marked by great originality, ingenuity in method, and wide scope, and their results are in many respects of basic importance. The first joint publications of the authors are as recent as 1939, and the extent of their accomplishment in so brief a period is remarkable.

The first section, dealing with spread of virus in peripheral nerves, supplies further and crucial proof that it is axon-conducted. The rate of conduction is measured, and the authors believe that it does not multiply in the axons themselves.

The strict specificity of poliomyelitis virus for nerve cells, at least in rhesus, is brought out in an admirably designed series of experiments, and the pathogenesis of lesions in the mesodermal-glial tissue of the central nervous system is discussed. The virus is strictly neuronotropic rather than neurotropic.

Study of the distribution of lesions in the central nervous system of rhesus and the chimpanzee after infection by various portals is followed by a comprehensive survey of the distribution in thirteen human cases and a comparison of the experimental and human disease. It is clear from their observations, as had been previously shown by Swan, Sabin and Ward, and others, that the olfactory route is not the usual one in man. It seems to the reviewer, however, that Case H8, in which lesions were present and marked in the secondary olfactory centers (the olfactory bulbs were not available for examination), may have been an example of olfactory entrance and certainly is not eliminated as a possibility. In view of the possibility of entry through the gut with spread through the sympathetics to the cord, as postulated by Toomey and others, it is a matter of regret that the authors did not include in their otherwise very thorough examination a study of the intermediolateral zone of the cord in which the sympathetic neurons are found, particularly since Swan and Környey failed to find conspicuous lesions in it.

A discussion of lesions in early arrested and nonparalytic poliomyelitis in experimental poliomyelitis is of considerable theoretic and clinical interest. In agreement with Sabin they find in such cases that many cells in the cord as well as in the brain stem are necrotic, but their explanation of the absence of paralysis is that cell destruction is too scattered to forfeit the function of any one entire muscle group. To the reviewer it seems likely (the assumption being based on the occurrence of minor degrees of chromatolysis in cells that are not actually destroyed) that another process also occurs in that temporary weakness and loss of function, common in the early acute stage of poliomyelitis, may be in part, at least, due to minimal, nonlethal infection of nerve cells from which they make complete recovery. It might also be well to mention a third possibility in "abortive" poliomyelitis raised by McClure's experiments, that infection may be limited to the peripheral ganglia and not reach the neuraxis itself.

Another series of experiments showing that the nerve cell may be rendered refractory to infection by previous injury to its axons suggest to the authors that sus-

ceptibility to infection (which also varies between different cell groups) probably depends on the internal metabolism of the cells. Their discovery that it can be artificially modified is promising.

Finally, the authors report studies which throw a good deal of new light on the question of immunity. They show that resistance to infection after an attack of the disease is limited to the actual areas infected; and that second infections in the same animal with the same strain of virus can be produced in areas previously uninvolved. It is a brilliant demonstration of local tissue immunity as opposed to general immunity (presumably humoral) which has occupied the attention and hopes of experimenters so long. Howe and Bodian conclude that attempts at prevention can be attempted along three lines: preventing the virus from reaching susceptible persons, arresting the progress of infection before it has reached the central nervous system, and limiting the spread of infection after it has reached the central nervous system. How the last two problems are to be approached in man is not clear.

This volume, published by the Commonwealth Fund, while primarily designed for those specializing in the basic problems of poliomyelitis, contains much matter of interest to the general reader. It is beautifully printed.

HAROLD K. FABER.